The New England
Journal of Medicine

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Volume 244 MAY 24, 1951 Number 21

THE SHATTUCK LECTURE

THE ROLE OF THE BASIC SCIENCES IN MEDICAL RESEARCH*

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I MUST first of all express my profound appreciation of the honour you have done me in inviting me to deliver this Shattuck Lecture. To be the first man from across the Atlantic to be asked to undertake this task is in itself a signal compliment, but for me there is a special feeling of pleasure in that you have thought fit to invite me, a nonmedical man, to address you on this occasion, when we have in mind the memory of a physician, a former president of this Society and a member of a great Boston medical family. In this I find once more evidence of the generous recognition accorded by physicians to those outside their profession who wish to devote such powers as they may possess to the advance of medicine.

It was indeed this thought that led me to the choice of my subject today. It appeared to me better that I should not address you on some special subject of research, on which I could not hope to speak without wearying you with technical matters of interest only to specialists, but rather that I should attempt to put before you some general considerations that seem to me to be of importance to medical research and therefore to the real advancement of the subject that we all have at heart. What you will hear from me I must ask you to accept as a personal view; it will be coloured by my own training and experience, by the preoccupations of my job as director of a research institute and by the conditions of scientific and medical work in my own country, which are so different from those prevailing in yours in spite of the traditions that we share.

I have spoken of the preoccupations of my job as a director. In saying this I had in mind one major preoccupation, namely, the preservation of the proper balance between the different parts of the general research effort that is under my care. In the institute under my direction the aim is to take some part in all aspects of medical research of a laboratory nature except for those types of work that are immediately concerned with the care of patients. This definition seems to be a clumsy periphrasis, but I am forced to use it in order to avoid applying to our own work the question-begging and pretentious epithet "fundamental," which is used so often and, in my opinion, with so little justification. The object of all research, pure or applied, is the acquisition of new knowledge, and it is by its fruits, be they theoretical or practical, that any research effort will ultimately be judged. Just as much damage may be done to the cause of science by the intellectual snobbery that arrogates to academic research the term "fundamental" as by short-sighted insistence on the direction of effort to immediately applicable results.

Even within the limits that I have laid down, the work of a large institute for medical research must nowadays cover a large proportion of the field of science. From the mathematics required for statistical work and the design of experiments we must range through physics, chemistry, physiology and biochemistry, pathology and bacteriology to research in pure experimental biology, because we have learned that at any time, from any one of these branches of effort, may come a discovery that will contribute to the general stream of progress. All this means that those who have an over-all responsibility for the conduct of the work must constantly be on the alert to introduce a new discipline or new technic that has a contribution to make; it is equally their duty to ensure that no technic is allowed to become an end in itself and that the development of each major division of the work is so controlled as to take its proper place in the framework of the total effort.

It is easy to express these ideals; it is a very different matter to live up to them. Complete success is, I imagine, beyond the reach of any individual. The best that the ordinary man who finds himself in the position of a director of research can hope for is that he will be able to retain a reasonable broadness of outlook and flexibility of mind, and above all that he may be blessed with the willing co-operation of his colleagues; he can do nothing unless the men with whom he works are prepared, while retaining their natural enthusiasm for their own subjects, to see other departments expand more than their own, and perhaps sometimes even at the expense of their own, if such a development is

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 23, 1951.

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necessary in the interests of the work of the institution as a whole. It is encouraging to find that the unselfishness that is demanded by this sort of cooperation is so often forthcoming.

I must now leave these generalities and approach the real theme of my discourse, which is the consideration of the role of the basic sciences in medical research. The very term "basic science" is an unsatisfactory one and requires more precise definition. We are frequently told, though in rather a different connotation, that science is one and indivisible. This truism does in fact convey the idea, which is perfectly correct, that no branch of science is truly independent of any other. Nevertheless, there are some disciplines in science that unquestionably derive more directly from first principles than others, and it is these that I mean to indicate by the word "basic." The branch of science that, from this point of view, is most truly to be designated "basic" is, I suppose, pure mathematics, for in this branch new advances are the result of reasoning from principles and do not depend on help from any other scientific discipline. Also possessing a high degree of independence are the theoretical aspects of physics and chemistry; when we come to the experimental development of these subjects we find that their individualities become less clearly marked, and that progress in one necessitates at least some general knowledge of the other; nevertheless, these sciences have grown for the most part through experiments based on the direct observation of natural phenomena, planned with the system of thought and carried out by the technic of the individual discipline. On the biologic side it can similarly be said that the sciences of botany and zoology, in their theoretical development, based on the observation of nature, are to a large extent independent and therefore basic; their experimental developments, requiring help from a multiplicity of sources of knowledge and technic, are another matter. Although no clear line can be drawn, therefore, I suggest that it is reasonable, so far as our subject is concerned, to make a distinction between those branches of science such as mathematics, physics, chemistry and the observational and theoretical aspects of biology on the one hand and the so-called medical sciences of physiology, pharmacology, pathology, bacteriology and so forth on the other. Those of the first group are *basic*, by virtue of their relative independence of development and of their close relation to first principles in nature; those of the second are *derived*, in that their development is almost entirely experimental and because the very nature of the experiments is determined by the principles of mathematics, physics and chemistry. At any rate, I must ask you to accept this rough classification, arbitrary though you may consider it, if only as a means of limiting the field with which I have to deal. In actual fact, my remarks will be concerned for the most part with chemistry, to a smaller extent with physics and very little indeed with mathematics. This restriction is imposed upon me by personal interest and by the limitations of my knowledge. I do not wish to suggest that the order in which I have named the subjects is necessarily that of their relative importance, but anyone dealing with a subject of this kind is bound to draw his examples from the field that he knows best.

In so far as I can still claim to be a scientist at all, I am a biochemist, trained chiefly in chemistry. This having been said, it is right that I should at once make a confession that makes it appear that I am very far from attaining the ideals that I have stated to be those of a good director of research: this is, that in our institute the largest group of workers is that of the biochemists, and that together with the chemists they comprise some 34 per cent of the total staff. I have spoken of the preoccupation that anyone in charge of a large research institute must feel concerning the preservation of a proper balance of the work. You may be assured that the figures that I have just mentioned cause me occasional qualms. Can it really be right that in an institute for medical research so large a proportion of the effort should lie in fields apparently so remote from the many medical problems crying out for solution?

Before considering in more detail the situation as we find it today, it may be worth while to consider the historical relations of medicine with chemistry and physics; there is no doubt that this relationship is an extremely close one, and indeed it might be argued that most of the development of modern medicine is due to the efforts that have been made from both sides to maintain and strengthen it. Let us consider some of the facts.

During the Middle Ages medicine stagnated for centuries. Observation, indeed, was keen and purely descriptive knowledge accumulated in large amounts, but understanding of function lagged, and treatment remained primitive and empirical. This state of affairs was largely due to the tradition of Galen, the weight of whose authority lay like a blanket on the minds of medical men, supplying them with a dogma that was only too satisfying and stifling any sparks of originality of thought. A revolutionary force was required before any real advance could be made. This was eventually forthcoming in the person of the iconoclastic genius Paracelsus, the first of the medical chemists. The characteristics of Paracelsus to which I suggest that the development of medicine owes so much are his intellectual courage and his insistence on the experimental method, so repugnant to the princely physicians who were content to rest in self-satisfaction on authoritarian teaching. The burning of the books of Galen, which Paracelsus is said to have done at his inaugural lecture as professor of medicine at Basel, may perhaps be dismissed as a

histrionic gesture in keeping with his flamboyant character. However, let me quote some words that he wrote, for these have the ring of sincerity: "I praise the chemical physicians, for they do not consort with loafers or go about gorgeous in satins, silks and velvets, gold rings on their hands, but they tend their work at the fire patiently, day and night. They do not go promenading, but seek their recreation in the laboratory, wear plain leather dress and aprons of hide upon which to wipe their hands, thrust their fingers among the coals, into dirt and rubbish and not into golden rings. They are sooty and dirty, like the smiths and charcoal burners, and hence make little show, make not many words and gossip with their patients, do not highly praise their own remedies, for they well know that the work must praise the master, not the master his work."

The passion of Paracelsus was for the application of chemistry to medicine, and above all for the use of pure chemical substances for therapy in place of the crude concoctions, based largely upon superstition, that were commonly in use. Even though he, and still more his followers in the school of iatrochemistry that he founded, were still under the influence of alchemical superstition and wasted great effort in the search for the elixir of life, may we not say that they had the root of the matter in them, and that they would have gloried in the modern developments of drug therapy as the final justification of their ideas?

The history of the association of chemistry with medicine after the time of Paracelsus has been a chequered one. His followers shared the characteristics of all revolutionaries; they were led by their enthusiasm into extravagances and claims of such manifest absurdity as to bring them into disrepute. The process perhaps reached its peak when Glauber designated the humble salt that still bears his name as "sal mirabile," the cure for all human ills. While this was going on, there was a great development in the schools of anatomy and physiology; the work done there, with its direct application to the human body, seemed naturally to offer a more direct and promising approach to the problems of medicine. As a consequence, it was not for a very long time, indeed not until nearly the beginning of the present century — that chemistry came into its own again as a full partner in medical research.

This is not to say that chemistry had not made its great contributions to medicine in the meantime. We have only to think of the late eighteenth and nineteenth centuries to realize this. Early in this period the work of the chemist Lavoisier laid the foundation for the understanding of the processes of metabolism. Late in the period the chemist Pasteur founded the science of bacteriology; throughout it new uses were being found for pure chemical compounds in medicine, and with the rise of the subject of organic chemistry the numbers of these compounds increased vastly. Nevertheless, there was no deliberate or concerted effort on the part of chemists to help the progress of medicine; the advances that were made, such as the introduction of anesthetics and the development of analgesics, hypnotics and many other valuable drugs, were due to the alertness of a few enterprising physicians in watching for those fruits of chemical research that might be of use to them in their work.

The change that has come over the scene during the last fifty years is so obvious as to need no emphasis. We have only to think of the vast body of knowledge that has been built up by chemical research on the hormones and the vitamins, of the origination and development of the whole subject of chemotherapy and of the great advances in pharmacology that have depended on the efforts of the chemist. These are all familiar to you and I have no intention of taking time to recount them in detail. Rather do I wish to consider the reasons for the change that has come about, and to discuss some of the less conspicuous ways in which chemistry is helping medical research.

It appears to me significant that the transformation that has occurred during the past half-century and that has brought us into a golden age for the chemist engaged in medical research coincides with the growth of biochemistry into the subject as we know it today. Just as organic chemistry grew up through the study of natural products of plant origin — their isolation, structural identification and sometimes their ultimate synthesis, so did the subject first known as physiological chemistry originate in a chemical interest in the components of the animal body. It seems to be a general characteristic of the development of the biologic sciences that the early stages are almost entirely descriptive, interest in function coming much later. This has certainly been markedly true of biochemistry. The early physiologic chemists analyzed tissues, separated their major components and characterized them generally from a chemical point of view; sometimes they went further and studied their constitution, but they left the question of their biologic function largely untouched; so long as this state of affairs lasted, physiologic chemistry could be little more than a poor relation of organic chemistry — poor because the intractable nature of the material led to much unsatisfactory work on ill-characterized substances. "Thierchemie ist Schmierchemie" was a sneer, perhaps, but one that hurt because it contained a large element of truth.

True biochemistry could not begin its proper development until the change of emphasis from structure to function had occurred. The man who, above all others, was responsible for this change was the English biochemist Frederick Gowland Hopkins. The importance of Hopkins' contribu-

tion lies not so much in his personal discoveries, far-reaching in their effects as these were, but in the efforts that he made all through his life, with eventual success, to promulgate a new view of his subject. Although he did not minimize the importance of the isolation and characterization of compounds of physiologic importance from the body, he regarded this part of the work as the necessary chemical preliminary to the study of matters of real biochemical interest. To him it was the study of the nature of the processes going on in the complex laboratory of the living cell that was the true function of biochemistry, and the chemistry of compounds that could be isolated from the animal body was only of interest in so far as it threw light on these processes.

This attitude has now become so widespread that it is difficult at first to realize how profoundly it has affected not only the growth of the science of biochemistry itself but the whole development of the application of chemistry to medical research. It has, for instance, been the stimulus behind the chemical work of the last twenty-five years on the hormones and vitamins. This work has been a monumental achievement in organic chemistry and can stand on its own merits as a contribution to that branch of science alone; its interest and importance for medicine are immeasurably enhanced by the increased knowledge of the mode of action of these physiologically active compounds that can be obtained when it becomes possible to experiment with them in the pure state and with full knowledge of their chemical structure.

I may perhaps be permitted to illustrate this point by referring to the problem that, in one form or another, has been a major subject of interest to me throughout my scientific life, namely, the problem of the biochemistry of the thyroid gland. The establishment of the chemical constitution of thyroxine and its synthesis were purely chemical pieces of work, complete in themselves; nor were they converted into biochemistry by the fact that they were necessarily preceded by studies of the isolation of thyroxine in the pure state from the natural source. From one point of view, as I have said elsewhere, the work on thyroxine that culminated in its synthesis could be regarded as merely confirming a fact that was already firmly established by other lines of evidence, namely, that the active principle of the thyroid gland was an organic compound containing iodine; regarded in this way it would be a satisfactory end-point.

Looked at biochemically, however, the matter appeared in quite a different light. Two matters of biologic interest were immediately raised by the chemical knowledge that had been gained about thyroxine — the mode of formation of the compound in the body and the mechanism of its action in the tissues; thus two large fields of work were opened up. The second of these two questions, the mechanism of action of thyroxine in the tissues, remains unsolved and still constitutes a challenge to biochemists; a general answer to the first question relating to the biogenesis of thyroxine was proposed in the early days of the chemical work and has finally been shown to be correct.

Like many problems in science, this one has been slow in solution. Different lines of circumstantial evidence were accumulated over many years; all pointed in the same direction, and when at last the availability of radioactive iodine made it possible to put the theory to a direct test in a manner that could not have been conceived earlier, the answer was clear and unequivocal. Here, therefore, we have an example of a piece of chemical work giving rise to a biochemical speculation that on being put to experimental test is in time proved to be well founded, and we are left in the end with a picture of the course of events by which a hormone is formed in the body — a picture that is more interesting and important to the biologist and medical man than is the actual knowledge of the chemical structure of the hormone itself.

The matter does not end there. On the one hand, the work that has led to the final proof of the biogenesis of thyroxine has itself raised other questions concerning the biochemistry of the gland that cry out for solution; for instance, we have still to explain the mechanism by which the thyroid carries out its characteristic and essential function of concentrating iodine. On the other, it is not unreasonable to claim that this work also contributed to the discovery of the antithyroid substances that have proved so important in the treatment of hyperthyroidism; it has certainly helped in the understanding of the mode of action of these compounds, and the knowledge gained by it has been of value in the development of the use of radioactive iodine for both diagnostic and therapeutic purposes. At long last, therefore, a piece of work of an academic organic-chemical type leads through biochemical development to applications in practical medicine.

Let us now turn to a quite different aspect of biochemistry, the development of which has again been largely due to the dynamic conception of the subject that we owe so largely to Hopkins, namely, the biochemistry of enzymes. The study of enzymes has, of course, been one of the richest fields of investigation for those interested in the course of biologic reactions, and the knowledge gained has transformed our conceptions of the chemical processes within the living cell. Of more immediate interest to us today, however, are the repercussions of studies of enzymes on research more directly connected with medicine. We may recall, for instance, that the mode of action of many vitamins is to be explained in terms of their specific action on enzyme systems essential to the normal life of the cell; this means that it is possible to define precisely the biochemical lesion that will result from a par-

ticular vitamin deficiency. Similarly, the action of drugs has frequently been shown to be exercised through their effects on an enzyme system; hence the drug can be used not merely to produce an overall effect but with precise knowledge of what it is doing in the body; surely there can be no greater help than this to the intelligent practice of therapeutics.

A further aspect of enzyme biochemistry that has turned out to be fruitful in quite unexpected directions is that of competitive inhibition of enzymes. The phenomenon was discovered many years ago and for a long time was regarded as having no more than academic interest. In the end, however, it inspired the Woods–Fildes theory of chemotherapeutic action and led to the discovery of the antagonistic action of *p*-aminobenzoic acid and sulfonamides. The influence of this work on chemotherapy has been very great and will certainly increase; although it has not yet led directly to any new drugs of outstanding practical importance, it has had the great virtue of introducing reasoned thought into a subject that was formerly on an uncomfortably empirical basis.

I have said that the application of thought on the lines of the Woods-Fildes hypothesis has not yet led directly to the production of chemotherapeutic agents of great practical importance. This is indeed true, although the actions of the folic-acid antagonists, which were investigated on the basis of this theory, give promise for the future. It is a curious and interesting fact, however, that one of the major chemotherapeutic contributions from Great Britain in recent years, the production of the antimalarial drug proguanil and of the antitrypanocidal drug antrycide by Imperial Chemical Industries, resulted from work deliberately planned on the basis of the theory of interference with essential metabolites. It is true that the successful drugs that ultimately emerged did not fit the original theoretical conceptions; nevertheless, one is tempted to feel that the small group of workers responsible for this research, which yielded returns much higher than the more extensive but more empirical efforts of the German chemical industry over many years, received the reward of virtue for the solid scientific thought that they had put into their project.

The mention of drugs reminds me of another example of an academic study in chemistry that has led, through pharmacologic and physiologic analysis, to results of unexpected importance to medicine. There are many such instances; I choose this one only because it is within my personal experience and because it is of topical interest. You will probably be aware that there has been for many years, in the National Institute for Medical Research, an interest in pharmacologic agents affecting the conduction of the nervous impulse. This interest was inspired by the work led by my predecessor, Sir Henry Dale, on the chemical transmission of nerve impulses, and it is worth noting in passing that this work itself was largely dependent for its progress on the success of chemists in isolating the essential compounds concerned. Now the organic chemical division of the Institute has as its main task the study of chemotherapy; in spite of this, owing to the very liberal conditions of choice of work enjoyed by members of the Medical Research Council staff, the chief chemist, Dr. Harold King, was able to indulge the predilection that he shared with many of his organic-chemical colleagues for work on alkaloids. In view of the work going on in the physiologic laboratories, it was natural that he should choose for study the alkaloids of curare, for it was well known that the toxic effect of this arrow poison was to block transmission at the neuromuscular junction.

The first significant result of King's work was the isolation of *d*-tubocurarine, the alkaloid responsible for the typical physiologic effect of tubocurare. This achievement itself was of immediate medical importance, for it made possible the production, under safely controlled conditions, of a state of muscular relaxation, combined with relatively light anesthesia, that is of great value in certain surgical operations. The matter, however, was not allowed to rest here; workers at the Institute and elsewhere were keenly interested in the relation of chemical structure to pharmacologic action, and speculation arose concerning the reason for the peculiar activity of *d*-tubocurarine. From the structure of the alkaloid, as revealed by King's work, it appeared that the situation of two quaternary ammonium groups at rather widely separated points in the molecule might be significant. This idea led to the synthesis of a series of simple compounds, — straight-chain aliphatic hydrocarbons having quaternary ammonium groups attached to the terminal carbon atom, — with a view to their pharmacologic examination. It was found that the member of the series containing ten carbon atoms (as it happens, the same number as separate the quaternary groups in *d*-tubocurarine) was if anything more active than the alkaloid in producing neuromuscular block. Subsequent physiologic analysis has shown that the mechanism by which this compound, decamethonium, produces the block is quite different from the true curare action; the over-all effect, however, is the same, and decamethonium has found its application as a substitute for curare.

More important still is the fact, revealed by systematic pharmacologic study of the whole series, that the members with five and six carbon atoms (pentamethonium and hexamethonium) are powerful autonomic blocking agents. This property opens up many obvious possibilities for their therapeutic use, and results of great promise have already been obtained in the treatment of hypertension and in

that of peptic ulcer, in which condition the secretion of acid can be almost completely suppressed. The development of the methonium drugs indeed promises to be a major advance in pharmacology. It began, as you have seen, with a purely chemical investigation, but we must realize that it could not have continued without the application of the particular mode of thought of those interested in the borderland between chemistry and pharmacology.

The few examples that I have given you will have to suffice to illustrate the point I am trying to make, namely, that there is almost unlimited scope in which chemistry can help medicine in the broadest sense, — not only when it is deliberately applied to definite medical and biologic problems but when it is carried out for its own sake, provided that this is done in the right environment. I am here giving the word "environment" a very comprehensive meaning; I am using it not only to imply close contact with research workers whose interests lie on the biologic side but also to imply that the chemists themselves should have the desire and the requisite mental attitude to see that the biologic aspects of their work are pursued. I have, as I initially said I would, deliberately avoided speaking of the obvious contributions of chemistry to medicine at the present time, such as those in chemotherapy, antibiotic research and the production of new drugs, apart from one or two special examples, since these things are in everyone's mind; I have also omitted all mention of such matters as the part played by studies of the physical chemistry of proteins in immunology and in connection with blood transfusion. These and many other omissions that will occur to you have been made only because of limitations of time. As it is, I have already devoted such a large proportion of this lecture to chemistry and biochemistry as to leave myself little space for other subjects, and in doing so I have exposed to you only too plainly my personal prejudices.

Let us now turn to the subject of physics. When one considers the application of physics to medical research the thought that immediately springs to one's mind is that this is a matter of comparatively recent development. One thinks of radiologic diagnosis and radiation therapy, the use of modern optical methods, electron microscopy, high-speed centrifugation, the use of isotopes in research and so on. The modern developments are indeed impressive, a fact of which the truth has been forced on my own attention; the plans for the new National Institute for Medical Research, which had been completed in 1939, had to be completely revised five years later in order to provide for physical technics that had been developed in the interval and were still on the increase. This was a formidable task and would not have been undertaken if all concerned had not been convinced that the new technics were necessary for the research that had to be undertaken.

Although the more spectacular applications of physics are modern developments, it is well to realize how much the progress of medicine in the past has depended on the parallel and continuous growth of physical knowledge. Acquaintance with the elementary principles of classical physics has now become so much a part of the mental equipment of an educated person that it is hardly any longer to be regarded specifically as scientific knowledge; it amounts to little more than an intelligent appreciation of the environment. Although this background of knowledge of elementary physics is now such a common possession that most people do not consciously realize that they have it, we have to remind ourselves that three or four hundred years ago this was far from being the case, and that the physical explanations of everyday phenomena that we take as a matter of course were then in process of evolution. The development of classical physics was particularly active in the seventeenth century and must have had a profound influence on workers in other branches of science; we can hardly suppose, for instance, that this intellectual movement did not play a part in the inspiration that led William Harvey to his discovery of the circulation of the blood.

Physics indeed so permeates the whole of scientific work that it is difficult to think of any major advance in knowledge of biologic function the conception of which has not made use of physical principles, even though the help of other branches of science has had to be called in before the picture could be completed. Examples of the sort of thing that I have in mind are the application of the laws of mechanics to functional anatomy, the use of the laws of heat transfer and of the relation of heat to mechanical energy in the explanation of the maintenance of steady body temperature, the study of the functions of the eye with the aid of physical optics, the constant use of the microscope and many other obvious instances of the kind, apart from definitely physical investigations such as the study of the electrical properties of nerve. It is therefore against a background of realization of the continuous and essential part that physics has played in medical science that I wish briefly to consider some of its more striking contributions at the present day.

Of these contributions the first that comes to mind, perhaps because it has the longest history, is that made by the discovery of x-rays. The medical possibilities of the discovery were realized as soon as Röntgen had made it, and in its subsequent development the x-ray method has of course become one of the most powerful diagnostic tools of the physician. Moreover, the therapeutic effects, discovered the hard way through much suffering and before the biologic properties of the radiation were

understood, have been exploited with great benefit to humanity. Now we find the possibilities of radiation therapy extended to an enormous degree by the development of particle accelerators. The ultimate benefits to be derived from this extension cannot yet be foreseen. It is, however, a remarkable commentary on the close bond that has been formed between physicists and physicians that as each new elementary particle is discovered and each new accelerating machine developed one of the first thoughts in the minds of both is of possible applications in the treatment of disease. Whether this is because radiation therapy is mainly directed against malignant disease, which inspires such peculiar dread in men's minds, I do not know; however that may be, I believe that the present state of affairs carries a warning that even a good process can go too far. The mutual stimulation of interest in radiation therapy by physicists and physicians is entirely desirable until enthusiasm begins to outrun judgment. Looking at the matter from outside, and observing what seems to be almost a sense of obligation to obtain for medical work each bigger and better particle accelerator as it becomes available before any serious biological experiments have been made, one sometimes wonders whether this stage has not been reached. To say this is not to argue that the medical possibilities of any new physical discovery should not be pursued to the limit; it is only to suggest a somewhat more cautious and experimental approach.

A less obvious way in which the discovery of x-rays has benefited medical research is through the development of x-ray crystallographic analysis. The importance of this lies in the information that it can give concerning the details of molecular structure, and the discoveries made with the aid of the method concerning the structure of high-molecular compounds, such as proteins and polysaccharides, have had a profound effect on biologic thought. Moreover, there is one case at least of a relatively simple substance — namely, penicillin — in which the ultimate refinement of x-ray analysis set the seal on a formula that was still in doubt on purely chemical grounds.

The mention of structure brings one's thoughts to the developments that have occurred in microscopy and that have made possible the examination of objects far beyond the resolving power of the ordinary light microscope. Two of these developments, namely the use of ultraviolet light and the discovery of the electron microscope, increase resolving power; two others offer advantages of a different kind to microscopy, the phase-contrast method making possible the direct microscopical examination of living tissues and the reflecting microscope offering a completely achromatic system. All these advances have made their contributions to medical research, particularly in cytology and cytochemistry and in the general field of research on viruses. None of the methods has reached anything like perfection, and all suffer from more or less serious drawbacks; there is no doubt, however, that as technical improvements are achieved they will make possible even more far-reaching studies in micromorphology; it is indeed the demands for this sort of work in medical research that form the main stimulus for their further development.

One of the most powerful new tools that medical research, especially in its biochemical aspects, has received from physics has been provided by the radioactive isotopes that have become available as the result of the discovery of nuclear fission. I have already referred to one problem in which this tool has been used with good effect. In general, however, the power that we now possess of labeling a compound and following the course that it takes in the body enables us to tackle and solve problems of intermediary metabolism and biosynthesis that were formerly totally insoluble. The results that have already been obtained are impressive and have given us new conceptions of many biochemical processes; when we consider that the method is still in its infancy, we may well wonder what is the end of the road along which it is leading us. Here again is an outstanding instance in which the physicist and the medical research worker mutually stimulate each other, and in which they must work in close contact if the best progress is to be made.

Finally we come to some more general physical methods. The application of these methods goes far beyond the field of medical research, but they have established themselves as necessities for the medical research worker. I am thinking particularly of ultracentrifugation, electrophoretic analysis and above all, perhaps, of chromatography. The ultracentrifuge has opened new fields of knowledge of the physical properties of proteins. By its revelations concerning their molecular weight it has enabled us to understand many features of the behaviour of the proteins in the body, particularly those of the blood, which are of the greatest importance in health and disease. The method of electrophoretic analysis, with its power of separating proteins from one another by virtue of their differing electrical charges, is able to reveal the presence of abnormal proteins in the blood and other body fluids; it has made it possible, furthermore, to identify the particular fraction of the blood protein that contains the antibodies. The ramifications of the method of chromatographic analysis are so many that it would be futile for me to attempt to enumerate them. Suffice it to say that in its various modifications chromatography has proved to be the most versatile and powerful analytical method that we have in our possession. With its aid we can separate compounds that are so closely similar in physicochemical properties that they cannot be torn apart by any other means, — and this we can do with quantities of a few milligrams. It is difficult to put

a limit to what this method may ultimately do for biochemistry and, through biochemistry, for medical research.

If we reflect for a moment on the few remarks that I have made about physics in medical research, we see that the situation is somewhat different from that that obtains in chemistry. Chemistry is linked with the biologic subjects through the intermediate discipline of biochemistry; physics, on the other hand, apart from the general fact, which I have emphasized, that the principles of classical physics permeate all scientific work, stands apart, and the help that it can give to medical research is more in the provision of new technics. This help is of the greatest value and may open entirely new fields of study, but the sharpness of the intellectual dividing line between the man who thinks in terms of physics and his colleague who has been trained as a biologist is an obstacle in the way of that close day-to-day collaboration that is so important in all research, and so specially important in medical research. Fortunately, men are to be found who can bridge the gap; for the future it is most important that they should increase in number. Otherwise it can happen that in the physics division of a biologic or medical research institute the workers remain essentially physicists, sometimes under the spell of their beautiful apparatus, and forget that they would not be in the institute at all but for the wholehearted share in the investigations of their biologic colleagues that is expected of them.

Of the three branches of "basic" science that I undertook to discuss in relation to medical research, I am now left with mathematics. What can I say of this? My ignorance of the subject is so profound that it is with the greatest diffidence that I say anything at all. I have, however, just enough knowledge to enable me to value highly the service that mathematics can give to medical research, and so far as this comes within my personal experience it is only right that I should attempt to assess for you the role of this most basic of all sciences in our subject.

There are two main directions in which I am conscious that mathematics has a contribution to make and is essential to our work. Both come under the general heading of statistics, since it is the mathematical methods of statistics that are employed; one concerns the design of experiments and the other, biological assay. There is no doubt that in the past there has been an enormous wastage of effort in biologic research because of failure to take into account the principles of design of experiments. Biologic material is essentially variable in its behaviour, and this may make it difficult to obtain an unequivocal answer to even a very simple question. Attempts may be made to surmount this difficulty simply by increasing the number of experiments and the number of animals involved in each. Too often, especially when more than one variable is involved, this sort of procedure has given the investigator a spurious sense of confidence based on the feeling that he has done a lot of hard work, and hence he publishes results with confidence, only to find that they will not stand up to the test of statistical analysis. It is in cases such as this that the mathematician trained in design of experiments can help. If the investigator had discussed his problem with a colleague so equipped at the outset he would probably have found that the experiments could have been planned, taking full account of the variable factors, in such a way as to give him an unequivocal answer to the question in which he was interested; moreover, he would almost certainly have found that the experimental work required was very much less than he had put into his unplanned and inconclusive research. Perhaps eventually all biologic research workers will be expected to have the mathematical equipment necessary to enable them to plan their experiments according to statistical principles. At present this is far from being the case, and it remains essential that they should have access to expert advice. It goes without saying that the situation is greatly improved if the statistician is himself a biologist engaged in experimental work.

Apart from laboratory work, the statistician has a vital part to play in the planning of enquiries designed to obtain information on medical matters affecting large populations. Such enquiries usually have to be made by questionnaire — and the construction of a questionnaire is no matter for the amateur uninstructed in statistics. Even though such a person knows quite well the questions to which he wants an answer he will almost certainly frame them wrongly, and he may even ask unnecessary or irrelevant questions that will make the final statistical analysis of the material difficult or impossible. I must emphasize again that I myself am totally uninstructed in these matters. I have, however, seen the planning of an extensive medical survey, and I was greatly impressed with the care and thought that the statistician gave to the project, although the point on which information was required was apparently quite a simple one.

The question of biological assay is one that has always been of particular interest to me at the National Institute for Medical Research, chiefly because of our responsibilities in connection with international biologic standards, and with the control of therapeutic substances the potency of which can only be estimated by biologic test. The first and fundamental principle of biologic assay is, of course, that it should always be done in terms of a standard preparation; only in this way can the error due to the inherent variability of the biologic material be avoided. Even when a standard has been set up, however, the assay of an unknown preparation in terms of it is not a simple matter; it requires properly planned experiments, carried out with care, and a final statistical assessment of

the results. The statistician has a vital part to play in this; it is he who decides on the plan of the assay, on the total number and grouping of the animals to be employed and on the grading of the dose, and it is he who makes the final assessment. It is because mathematicians have interested themselves in matters of this sort and because pharmacologists have been educated to appreciate the statistical principles of biologic assay, that physicians are able to place such implicit reliance on the stated activity of many of the therapeutic products that they use. The availability of such accurate information is not only of obvious practical importance in the proper treatment of patients: it is also an essential requirement for physiologic and pharmacologic investigation of the products in question. The provision of this information, for which we depend ultimately on the mathematician, lays still further emphasis, if such be needed, on the importance of his role in medical research.

Whatever the effect of my remarks may have been on you, I have talked myself into a frame of mind in which by now I have few qualms about the proportion of the total effort in our institute that is devoted to chemistry, biochemistry and physics. I shall assume that, for the time being at least, I have persuaded you to the same way of thinking and shall conclude by putting before you a general consideration that seems to me to arise from what I have said.

It would, I suppose, be difficult to find a physician who would not assert with pride and confidence that his profession is founded on science. How many physicians, while making this assertion, can look back to their student days and honestly say that they had always appreciated this fact? In my country, at least, the proportion would not be very high. It is natural enough that this should be so. The average student starting on his medical course wants above all to become a doctor as soon as possible. He is faced with years of study of scientific subjects before he comes into contact with a patient, and although he knows theoretically that his later work is founded in principle on the scientific subjects he is studying he finds the drudgery of these, especially perhaps chemistry and physics, well-nigh unbearable. Little wonder, then, that we see him like Jaques' schoolboy "creeping like snail unwillingly to school" and when he gets there having little objective beyond passing the necessary examination as soon as possible so that he can get on with the things that he really wants to do.

Now, by any reckoning, this is a pity. You may say that later on the student or the qualified man will come to know better and will be ready to appreciate the true value of science. I agree that he will learn to make use of the fruits of science, but this is not quite the same thing. What he may not learn, and what seems to me equally important, is to appreciate the value of the scientific method. This can only be done by real submission to the scientific discipline.

We are all familiar with the attitude of many practicing physicians toward their colleagues who spend their lives in research. They themselves are intensely busy men, dealing constantly with practical matters, carrying a heavy load of responsibility and exposed to all the buffets and anxieties that a man must face when he practices his profession in a competitive world. We cannot, therefore, be surprised if the practitioner, although paying lip service to the intellectual attainments of his colleague in research, regards him in his heart as rather a poor fish. There the research man sits, he thinks, with a secure salary, protected in his ivory tower from the rough-and-tumble of the world and with nothing to do but the work of his own choice; has not such a man chosen the easy way?

Indeed he has not, as anyone who has had personal experience in research very well knows. It is true that he is sheltered from the world, but his task is an exacting one. Much of his effort ends in frustration and disappointment, and he is largely denied the immediate satisfaction that comes from the visible result of a practical task well done. It is indeed not uncommon to find men for whom the psychologic strain of full-time research becomes too great and who seek refuge in work of which the immediate results are more apparent.

In speaking of this common misconception of research work, I have again been thinking of my own country, but I suspect that similar misconceptions are not unknown here. In so far as they exist, they do so, I believe, because many practicing physicians have completed their education without ever realizing what research work really means. Perhaps they can never truly realize this unless they take part in it themselves. I believe myself, however, that it should be possible for them to learn to appreciate research in medicine, not only in terms of the spectacular achievements of which they can make immediate use but in terms of the continued effort, in branches of science apparently remote from medical practice, that will prove in the course of years, as I have tried to show that it has done in the past, to be of inestimable benefit to their profession.

If this could be achieved there is no doubt that progress would be even greater than it is now. The momentum of medical research has become so great that it will in any case continue, and a large part of this momentum is due to the motive of the workers concerned, whether medically qualified or not, which is the genuine desire to devote their efforts to what they believe to be the true advance of medicine. Few, however, are entirely indifferent to the opinion of others, and the efforts of the research worker will be more determined and more fruitful in proportion as even his most academic investigations are appreciated by his practicing colleagues.

BENIGN PAROXYSMAL PERITONITIS

Surgical and Histologic Findings*

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RECENTLY, Reimann[1, 2] has collected a group of disorders recurring with rather regular periodicity over many years without otherwise affecting the general health. In different persons the episodes are characterized by different features that, in the person affected, remain remarkably constant in the recurrent attacks. He has classified the disorders into four groups on the basis of the outstanding feature in the attacks; for the whole group of disorders he has proposed the term "periodic disease." The groups are periodic fever, periodic abdominalgia (benign paroxysmal peritonitis), periodic (cyclic) neutropenia and periodic (intermittent) arthralgia. Theories concerning etiology are reviewed and the evidence for either an infectious, allergic, endocrinologic or neurologic basis is inadequate. Reimann[2] believes that this whole group is best regarded as a manifestation of a rhythm of life.

In this presentation we are primarily interested in the entity called benign paroxysmal peritonitis, or the "periodic abdominalgia" of Reimann. Siegal[3-5] has presented a total of 17 cases of this entity, which is characterized clinically by recurrent bouts of abdominal pain and fever. The temperature may range from 100° to 105°F. During the attack there is very definite abdominal pain and tenderness. The diagnosis of "acute abdomen" serves to describe some of the attacks, and involuntary spasm of the abdominal muscles, as well as rebound tenderness, may be present. Nausea, vomiting, malaise and leukocytosis may be found. The localization may be variable or the pain and tenderness may involve the abdomen diffusely. Chest pain of a pleuritic nature may precede or accompany the attack of abdominal pain. The attack usually is of two to three days' duration but may be longer. The attacks usually begin early in life, occasionally in childhood, and continue at either regular or irregular intervals of weeks or months for many years. Between attacks the patient may enjoy good health.

Siegal[4] indicated that all diagnostic studies have been fruitless. He stated that in all the published cases in which ethnic data are given the patients have been either Jewish or Armenian, with the former race predominating. A review of Reimann's cases[2] on this point adds support to this belief. Although Siegal has presented evidence that the condition is suggestive of an allergic condition, he admits that the data are not conclusive.

The reported operative findings in this entity are sparse but add support to the idea that peritonitis is present. Siegal[4, 5] reported findings at laparotomy during attacks in four patients. In one case there was widespread edema of the peritoneum with a small amount of free fluid, which findings were believed to represent a nonsuppurative peritonitis. In two other cases the operative findings were also thought indicative of a chronic peritonitis. In the fourth case[5] stringy fibrinous exudate was present in the peritoneal cavity and microscopical examination of the peritoneum and omentum revealed acute purulent inflammation. Cultures of this material were negative. In one of the cases (No. 10) of Reimann,[2] peritoneal adhesions and free fluid suggested a chronic form of peritonitis. Siegal[4] has stated that no data are available (with the exception of his one case[5]) concerning the pathology, cytology or bacteriology of the peritoneum or its exudate. Some of these deficiencies in the knowledge of this curious entity have been remedied in the case that we have encountered and studied.

CASE REPORT

A 38-year-old veteran of Italian descent was admitted to the Diagnostic Center in order to determine the nature of his condition. He complained of abdominal pain that occurred in periodic attacks. He had served in the Army for three years. His mother and father had both been born in Italy and were over 60 years old, alive and well. Two brothers and two sisters were living and in good health. None of them had a similar condition or any other type of disease.

This patient stated that his attacks of pain began when he was 10 or 12 years old. In the beginning the attacks occurred about twice a year, but they had gradually increased in frequency. During adolescence the attacks occurred three or four times a year. During his army service the attacks occurred once every four to five months. In the past few years, he stated, the attacks had been occurring more frequently, on an average of every eight to ten weeks. These attacks lasted from two to three days, although after the first day they were not so severe. In the typical attack, the pain started in the right lower anterior or lateral chest. There was a gradual radiation of this pain into the right upper and lower abdomen, and it then seemed to settle in the middle of the abdomen. While the pain was at first more severe in the right lower quadrant, it gradually became diffuse. About four hours elapsed from the time the pain started in the chest until it was generalized in the abdomen. In the abdomen the pain often became very severe, and had been so severe that he had doubled up during attacks. In some attacks the acute pain lasted twelve to fifteen hours, although the dull ache that followed would often remain for two days. The pain was occasionally accompanied by nausea and by occasional but infrequent vomiting. He stated that during the attacks he ate soup and some liquids once or twice a day but nothing else. In the interval between the attacks the patient was in good health. He had had no diarrhea, but during the attacks he did not usually have any bowel movements. In the intervals he had noticed some tendency toward constipation. He had not noticed any particular food or substance that caused

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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him discomfort. He had no hematemesis or melena. He claimed that milk caused diarrhea but did not bring on the attacks. He therefore did not drink much milk.

In the past, during these attacks, he was given various medications, without alleviation of pain. However, he had no hypodermic medications. During an attack that occurred when he was fourteen years old, one doctor thought that he might have had pleurisy. Other diagnoses that were made were gastritis and conversion reaction. During his army service diagnoses of intercostal neuralgia and of an undiagnosed condition manifested by abdominal pain were made.

He smoked cigarettes and drank moderately. His alcoholic consumption was generally of beer; this had not precipitated the attacks. Before he entered the army he worked as a chrome plater. In the intervals between attacks he was able to work without any difficulty. He worked at covering metals electrolytically with coatings of nickel, copper and other metals. He also mixed acids for pickling, and occasionally operated a buffing machine. During this period of employment his attacks of abdominal pain were no more frequent than they were previously or since.

In 1936 an appendectomy was performed in his home town during one of these attacks. The records of that hospitalization were obtained and revealed that he complained of severe cramps on the right side that had begun ten years prior to admission and had occurred periodically, lasting two to three days, during which the patient stopped working. The pain would gradually subside. The microscopical diagnosis was acute appendicitis.

He was hospitalized from November 1 to November 16, 1943, during his army service because of one of these attacks. The examination made during this attack revealed hyperperistalsis with increased intensity of the bowel sounds. Examination of the abdomen revealed muscle spasm of both recti, with direct and rebound tenderness, which was most marked in the epigastrium. After two days the examination was completely normal. At that time x-ray films of the genitourinary tract, a gastrointestinal series, a barium-enema examination and a cholecystogram were negative. A blood count at that time showed 9200 white cells per cu. mm., with a normal differential. The final diagnosis was "observation for abdominal pain, no disease found." A complete genitourinary study authorized by the Veterans Administration was performed on March 17, 1948, and no disease was found in the genitourinary tract. At that time routine laboratory studies, gastrointestinal series, and cholecystogram were reported to be negative. The final diagnosis was conversion reaction, mild, chronic. Because of the rather bizarre history in this case, the patient was referred to the Diagnostic Center for further study.

General physical examination on admission here was within normal limits. Examination of the abdomen during a period when the patient was free of symptoms was not remarkable. There was no tenderness on deep palpation, and no viscera or masses were palpable. Over the well healed, rather large right-lower-quadrant scar there was some tenderness on deep palpation. No rigidity or spasm was noted.

On the ninth day after admission he had an attack of pain that commenced in the right lower chest and radiated down into the abdomen. There was voluntary spasm of both recti, with some rigidity. Peristalsis was hyperactive, and there was marked rebound tenderness. On gentle palpation tenderness and pain were elicited. Examination of the lungs at that time was negative. During a twelve-hour period the temperature rose to as high as 102°F. On the next day it was 98.6° F. It is also interesting to note that on admission on May 9, 1949, the patient's white-cell count was 7900 with a normal differential, and the sedimentation rate 13 mm. per hour. However, on the day of his attack, the white-cell count was 13,200 per cu. mm., with 78 per cent neutrophils, 7 per cent of which were stab forms, 20 per cent lymphocytes, 10 per cent monocytes and 1 per cent eosinophils. The sedimentation rate was 20 mm. per hour. On the next day his white-cell count was 8700, with 55 per cent neutrophils, 41 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. It was during this attack that he was seen by members of the Surgical Service; it was thought that a laparotomy might be indicated. He was transferred to the Surgical Service and observed. During this attack a flat plate of the abdomen was obtained. Some loops of distended small bowel were observed, but this condition was not marked and was not consistent with an obstruction of the small intestine. It was during this attack that the diagnosis of benign paroxysmal peritonitis was suggested. The surgeons wished to operate, but the patient refused. After twenty-four hours he was returned to the Diagnostic Center. After the attack he did exceedingly well. He was free of symptoms and had no complaints for a period of twenty days.

The routine laboratory studies were within normal limits. The blood sugar was 105 mg. per 100 cc. The urine was negative on several examinations. Gastric analysis revealed 5 and 8 units of free hydrochloric acid two hours after administration of histamine, the other specimens showing no free hydrochloric acid. Many stool examinations were negative for blood, ova and parasites. An electrocardiogram was normal. An upper-gastrointestinal series, an intravenous pyelogram, a barium-enema examination, a cholecystogram and a chest plate were all negative. A blood Kahn test was negative. The nonprotein nitrogen was 27.8 mg. per 100 cc. A twenty-four-hour urine specimen revealed the porphyrins to be 6.5 microgm. per 100 cc. or 42.25 microgm. per total specimen. Serum-amylase determinations were within normal limits. A battery of liver-function tests was repeated several times during the course of his stay; all tests were within normal limits. This battery of tests included bromsulfalein, cephalin flocculation, thymol turbidity, prothrombin time, serum bilirubin, serum alkaline phosphatase and cholesterol with cholesterol esters.

On the evening of his twenty-ninth hospital day the patient left the hospital on a pass and drank six beers. During the next morning he felt well, but at about 1 p.m. he began to have pain in the right lower anterior chest. This radiated in typical fashion to the right side of the abdomen, right lower quadrant and right upper quadrant, and in about two hours he had generalized abdominal pain. About four hours after the onset of the attack, rigidity of both recti was noted, with marked tenderness and pain on gentle palpation in the right upper and right lower quadrants. There was marked rebound tenderness. The white-cell count was 18,950, with 91 per cent neutrophils, 26 per cent of which were band forms. His temperature reached 103°F. The serum-amylase activity was 63 Somogyi units per 100 cc. No eosinophils were noted in the blood smear, and a total eosinophil count was 97. Chest x-ray examination was negative, and the flat plate of the abdomen revealed some gas in the small intestine. The patient was seen by Dr. Gordon Lee, chief of the Surgical Service, who remarked at the examination that if he had not been familiar with the history he would have had a clinical impression of acute cholecystitis. In the interval between attacks, the patient had agreed to an operation if another attack occurred, and exploratory laparotomy was performed by Dr. Lee. (A description of the surgical findings will be found below.) The postoperative course was uneventful, with the temperature reaching a normal level two days after surgery.

Twenty-two days after the onset of the attack for which he was operated on, abdominal pain recurred and the temperature rose to 101°F. This attack lasted only one day. The patient was discharged from the hospital on the sixty-ninth day after admission.

From information obtained from his private physician it was learned that the patient experienced three attacks for which he was hospitalized in the six-month period after discharge. The patient wrote that he had had several other attacks for which he was not hospitalized and was losing a great deal of time from his work. The attacks were typical, with fever, abdominal pain and white-cell counts ranging from 18,000 to 20,000.

His physician reported the use of sulfadiazine and penicillin for one attack, streptomycin for another and a combination of aureomycin and Chloromycetin for a third. The patient was free of symptoms after two days, which is the usual length of duration of the untreated attack.

The most recent communication from the patient was received in November, 1950, during which month he had another attack. He stated that he had not had an attack since February, 1950. This remission period of nine months was longer than he had experienced in recent years. He was unable to work for three days as a result of the last attack, which he described as mild. Apparently the combination of antibacterial agents exhibited has not affected the basic etiologic process.

Surgical Findings

On opening the peritoneal cavity a moderate amount of cloudy fluid was noted and was aspirated into sterile tubes. The stomach, duodenum, small and large intestines, pancreas and spleen were essentially normal. A fibrinopurulent exudate was noted over the dome of the liver and on the parietal peritoneum. No adhesions were noted on the rest of the abdominal viscera. No lymph nodes were felt in the preaortic region, and there were no enlarged lymph nodes in the mesentery or greater omentum. Biopsies of the liver, parietal and visceral peritoneum, omentum and rectus abdominis muscle were obtained.

Total Eosinophil Counts

Since allergy has been mentioned in previous presentations as a possible cause of this condition, consideration was given to the eosinophil count, which is commonly increased in allergic states.

TABLE 1. *Total Eosinophil Counts.*

DATE	WHITE-CELL COUNT	EOSINOPHIL COUNT	REMARKS
5/31	6,500	138	No symptoms
6/2	6,500	250	No symptoms
6/5	18,950	97	At the height of an attack
6/7	12,000	150	36 hr. after surgery
6/11	11,700	234	Mild attack
6/21	7,500	158	No symptoms

Siegal[4] commented that eosinophilia was not found in any of his cases. None of the cases of benign paroxysmal peritonitis reported by Reimann[2] were characterized by eosinophilia. However, all previous reports of the eosinophil counts were based on the usual differential count of the stained blood smear. In this case the more accurate and dependable total eosinophil count was done, both during an attack and in the interval between attacks. Table 1 lists the total eosinophil counts obtained.

It will be noted that there was no increase of eosinophils during an attack. As a matter of fact, when there was leukocytosis the eosinophils were decreased in number. At the height of the severest observed attack the white-cell count was 18,950 per cu. mm., and the eosinophils numbered 97 per cu. mm., a decrease that is to be expected when a nonspecific noxious stimulus occurs in a patient with normal adrenal glands. It is our opinion that this finding of a lack of increase of eosinophils during the attack casts considerable doubt on the allergic theories of causation of this condition. Furthermore, examination of the peritoneum and its exudate did not reveal tissue eosinophilia.

*Bacteriologic and Histologic Findings**

Blood, bone marrow and peritoneal fluid obtained during the height of an attack were smeared and cultured. No bacterial growth was isolated on aerobic and anaerobic media. All smears were negative for organisms. Smears of the peritoneal exudate revealed many polymorphonuclear cells but no eosinophils. The peritoneal exudate was inoculated into guinea pigs and mice, with negative results.

FIGURE 1.
Liver revealed extensive fatty metamorphosis. The capsule is thickened and infiltrated with polymorphonuclear leukocytes (x200).

The liver biopsy revealed extensive fatty metamorphosis (Fig. 1). The fat was deposited in all portions of the liver lobule. The capsule showed moderate fibrous thickening and focal areas that were infiltrated by moderate numbers of inflammatory cells, which were predominantly neutrophils.

The rectus abdominis muscle showed variation in the intensity of the staining reaction of the muscle fibers but was not otherwise remarkable. The fat

*We are indebted to Dr. Henry Rappaport, formerly chief, Laboratory Service, for these data.

lobules of the omentum were frequently covered by fibrous adhesions, some of which appeared delicate and recent, others more dense and older (Fig. 2). These adhesions contained inflammatory cells, usually neutrophils or mononuclear cells.

The peritoneum over the right diaphragm opposite the liver showed fibrosis and fibrinoid

FIGURE 2. *Omentum Covered by Adhesions (x100).*

thickening as well as fibrous adhesions (Fig. 3). Within these adhesions there was an abundant cellular infiltration consisting chiefly of neutrophils. Some focal accumulations of cells were very dense.

The peritoneum of the anterior abdominal wall demonstrated focal areas covered by fibrinoid material in which erythrocytes and numerous neutrophils were enmeshed. Pale blue oval or irregularly shaped bodies about the size of a large macrophage appeared to be composed of foreign material. Double refractile foreign bodies, the significance of which is not understood, were seen within the superficial exudate. Many of these double refractile bodies appeared crystalline and varied in size and shape. Special stains revealed no bacteria.

On the basis of the histologic findings, diagnoses of acute peritonitis of undetermined etiology and fatty metamorphosis of the liver were made.

DISCUSSION

It is interesting to note that despite the many attacks experienced by the patient, the surgical and histologic findings were fairly well localized to the peritoneum in the vicinity of the liver. The adhesions were not marked or widespread, and the process was more acute than chronic. No enlargement of the lymph nodes was discerned. It will be recalled that chest pain, often of a pleuritic type, was usually the first manifestation in an attack, followed shortly by abdominal pain in the right upper quadrant, which soon became generalized. It is believed that this course is explained by the acute inflammatory reaction involving the peritoneal covering of the diaphragm adjacent to the dome of the liver.

FIGURE 3.
Peritoneum over right diaphragm opposite liver revealed fibrosis and fibrous adhesions with abundant cellular infiltration (x300).

The finding of rather extensive fatty metamorphosis of the liver was unexpected; it has not been

previously reported in this condition. Hepatomegaly or jaundice was not found at any of the many examinations. Many liver-function tests prior to and subsequent to operation were within normal limits. As Himsworth[6] points out, fatty infiltration of the liver is found in many conditions associated with malnutrition and chronic disease, among which are chronic febrile conditions. The role played by the liver in this disease is not known, and the finding of fatty metamorphosis seems to shed no light on the mystery of causation.

There is no question that in this case there was an acute localized peritonitis accompanied by fever and leukocytosis. In this respect we are in agreement with Siegal's criticism[5] of Reimann's designation[2] of this entity as "periodic abdominalgia," which signifies only recurrent abdominal pain. The term "benign paroxysmal peritonitis" is more in keeping with the actual clinical findings indicative of peritoneal irritation and the histologic findings, as recorded in the present case. It is our opinion that the designation of "benign paroxysmal peritonitis" should be reserved for cases with a long history of recurrent attacks characterized by fever, abdominal pain, leukocytosis and definite clinical findings of peritoneal irritation.

In the present case the patient was of Italian parentage on both sides of the family, which adds another ethnic strain to the two ethnic groups (Jews and Armenians) previously reported. Although the characteristics of the attacks point to an inflammatory origin, the rather localized acute condition found at operation after nearly twenty years of these attacks is somewhat unique. The rapid onset and disappearance of symptoms, with complete well-being in the intervals, would also be unusual in a bacteriologic process. The negative results of the bacteriologic studies of blood, bone marrow and peritoneal exudate during a severe attack and the failure of response to drugs that have a wide range of antibacterial activity are evidence against an infectious etiology of this condition. The results of the studies outlined above also argue strongly against an allergic causation. Until a more definitive causation is reached, we believe that consideration of benign paroxysmal peritonitis as one of the periodic diseases of Reimann is warranted.

Summary

A case of benign paroxysmal peritonitis occurring in an Italian male is presented. The findings at operation that indicated an acute localized peritonitis correlated well with the clinical findings of diffuse abdominal pain, fever and evidences of peritoneal irritation. The clinical course is discussed, as are the theories of causation by infectious or allergic agents. The absence of blood and tissue eosinophilia and the finding of fatty infiltration of the liver are also discussed.

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THE TREATMENT OF ESOPHAGEAL DIVERTICULUM BY INVERSION*

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THE treatment of esophagopharyngeal diverticulum continues to be an interesting surgical problem. For the majority of practitioners interest in the subject arises out of the comparative rarity of the condition and the fact that the diverticulum may masquerade under the guise of chronic laryngeal disease or vague dysphagia for many years.

The problems associated with the surgical treatment of esophagopharyngeal diverticulum are due to the fact that the esophagus withstands surgery poorly and that the location of the diverticulum allows any postoperative infection direct access to the mediastinum. These two factors have resulted in a careful and slow surgical evolution in developing an operation that would cure the condition and yet be safe for the patient. The two-stage operation so well developed by Lahey[1] in this country meets both these criteria. There has been a decided trend in the past few years, however, with the increased use of antibiotics, toward the more frequent use of a one-stage procedure for the removal of the diverticulum. Complications resulting from either of these procedures are still more frequent and more serious than a review of the literature would lead one to suspect.

The operation whereby the diverticulum is treated by inversion into the pharynx was first used by Girard[2] in 1896. After a series of fatalities resulting from the then accepted method of treatment, he was led to employ this method, having observed that certain large esophageal polyps were tolerated in the pharynx without discomfort to the patient. He reported a series of two cases, the first of which was complicated by a huge goiter. This case subsequently developed a slight wound seepage, which he attributed to suturing too tightly the base of the diverticulum. His second case was an uncomplicated diverticulum, and recovery was complete and uneventful.

He was careful to advocate the method for small diverticula only; if the diverticulum was large he advocated resecting all but 3 cm. of the pouch, closing the opening in the diverticulum and invaginating it into the esophagus. This operation by inversion has continued to be used extensively in Europe up to the present time. It is difficult to understand why the operation has not been more generally accepted by the surgeons of this country, in view of the fact that the risk of infection from an open esophagus is thus entirely avoided.

In 1934 McClure[3] reported a case that was treated by inverting the diverticulum into the pharynx by means of a catheter sutured to the bottom of the diverticulum, the catheter with the attached diverticulum being drawn up into the pharynx, from which it was removed on the following day by means of a tonsil snare. Recovery was complete and uneventful.

In 1944 Ross[4] made a brief survey of the literature and technic of the inversion operation and reported a series of three patients treated by this method, all of whom made complete recoveries without complications.

Anatomy

Figure 1 shows a diagrammatic view of the posterior wall of the pharynx and the upper portion of the esophagus. The posterior wall of the pharynx is almost entirely covered by the three constrictors, the superior, middle and inferior. Of these three we are most concerned with the inferior. An esophagopharyngeal diverticulum is a true herniation of the mucous membrane of the esophagus through the wall of the pharynx. It may occur in several areas. In the majority of cases, however, it occurs in an area situated more or less posteriorly at the junction of the oblique and circular fibers of the inferior constrictor of the pharynx. These lower transverse fibers of the inferior constrictor are commonly known as the cricopharyngeus muscle. This is the muscle that shuts off the pharynx from the

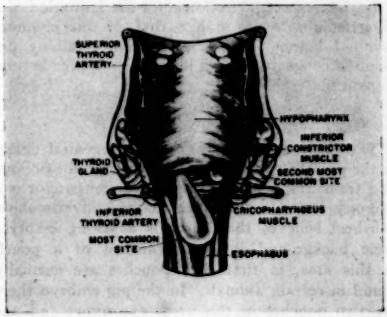

FIGURE 1. *Diagrammatic View of Posterior Wall of Pharynx and Upper Portion of Esophagus.*

*Presented at the annual meeting of the New England Surgical Society, Vergennes, Vermont, September 15, 1950.

†Attending surgeon, Brightlook and St. Johnsbury hospitals and Fitch Clinic, St. Johnsbury, Vermont.

esophagus during swallowing — the so-called cricopharyngeal pinchcock.

It is also in this area, that is, between the oblique and transverse fibers of the inferior constrictor, that the muscle gives passage to branches of the recurrent laryngeal nerve and a branch of the inferior thyroid artery, a small anatomical supporting defect thus being always present in this area. This weak point in the wall of the pharynx is believed to be developed into a true hernial protrusion by the complex mechanism involved in the act of swallowing.

Normally, when a person swallows, the cricopharyngeal pinchcock shuts off the esophagus from the pharynx until sufficient pressure is established in the pharynx to force the bolus of food into the esophagus. When, however, because of disturbed physiology, neuromuscular inco-ordination exists between the cricopharyngeus and the inferior constrictor with the result that the cricopharyngeus fails to relax, abnormal pressures may be created in the pharynx. This would tend to force any protrusion of the esophageal mucosa through the weak spot in the posterior pharyngeal wall, thus establishing the beginning of a diverticulum.

In this respect, the etiology of the formation of a diverticulum is not unlike that of our common inguinal hernia, in which repeated straining develops a congenital defect into a well-defined hernial protrusion.

Etiology

The presence of a pre-existing congenital defect in the posterior pharyngeal wall between the oblique and transverse fibers of the inferior constrictor is a primary factor in the formation of a diverticulum. Mosher[6] believes that there is a strong embryologic background in the formation of a pouch in this area, in that such pouches are normally found in certain animals. In the pig embryo there are two pouches in this area, one upper and one lower, the latter one persisting after birth. In the human embryo, at a corresponding stage, there are two similarly placed pouches, both of which disappear at birth. It is not difficult to believe that an anlage of this pouch might persist after birth and serve as a basis for diverticular formation. Further evidence of the existence of a congenital pouch is given by a case reported by Rush and Stingily[6] of a large diverticulum that was found to be present at birth and arose in this location.

Dunhill[7] has reported a series of six cases in one family, occurring over a period of three generations. Dinsmore[8] has reported two cases occurring in brothers. Wyllie and Blair[9] lend further credence to the congenital theory of diverticular formation by reporting a case in a two-year-old child. Jackson[10] has reported a case in a child of eight.

Age

The majority of reported cases have been observed in patients over fifty years of age. The average age of the 276 patients reported by Moersch and Judd[11] was 57.2 years. In 288 cases reviewed by Jackson[10] 90.6 per cent of the patients were over sixty years of age. This suggests that as the patient grows older, with a concomitant relaxation of his tissues, the pre-existing congenital defect is less and less well supported, with the result that a diverticulum is eventually produced.

Inco-ordination of the Cricopharyngeal Pinchcock

It is difficult to estimate precisely how much this factor contributes to the development of a diverticulum, inasmuch as any spasm of the cricopharyngeus should seemingly be associated with some difficulty in swallowing. However, many cases of diverticulum have been reported that were entirely asymptomatic and were discovered accidentally. Furthermore, operation does not correct muscular inco-ordination, and if it existed before the operation as a causative factor it should persist afterwards. Yet these patients are completely symptom-free once their diverticula are removed, and recurrences are not frequent.

Negus[12] believes that the cricopharyngeus is the sole etiologic factor in the development of these diverticula. His work, which includes an exhaustive study of the comparative anatomy of the larynx and pharynx, shows that in the lower animals this muscle actually functions as a true sphincter in preventing esophageal breathing. In man its sphincteric action is retained to a somewhat lesser degree. He believes that in the presence of inflammation, such as chronic hypopharyngitis and other inflammatory lesions involving the cricopharyngeal area, the sphincter may become definitely spastic and fail to relax. He suggests that lack of relaxation of the sphincter may also be due to nervous inco-ordination or to a deficiency in sensory stimuli. Thus the bolus of food is caught between the spastic cricopharyngeal sphincter below and the rigid larynx in front and is compressed laterally and superiorly by the inferior constrictor. This results in the exertion of abnormal pressures on the unsupported area lying posteriorly between the lower border of the inferior constrictor and the cricopharyngeus, the common site of diverticulum formation. His work seems definitely to establish spasm of the cricopharyngeal pinchcock as an etiologic factor in the formation of a diverticulum if not as its primary cause.

Eating Habits

Rapid eating is considered by Jackson[10] to be one of the major contributing factors in the formation of a diverticulum; it was observed in 82 per cent of his cases. Hasty eating usually results in imper-

fect chewing of the food and in the gulping of large boluses of food that by virtue of their size alone would bring abnormal pressures to bear on any pre-existing defect in the pharyngeal wall.

Inasmuch as the majority of reported cases occur in elderly people who either have lost many teeth, have artificial dentures or have no teeth, it is easy to believe that imperfect mastication might be a contributing factor. If inco-ordination of the crico-pharyngeal pinchcock did exist, it is conceivable that hasty eating and swallowing might well aggravate the condition. It would seem, then, that when an elderly patient has false teeth and is a rapid eater the ideal situation exists for the formation of a diverticulum if a congenital defect is present.

Symptoms

The symptoms of an esophageal diverticulum may vary greatly. There may be no symptoms, in which case the diverticulum is discovered by accident, or symptoms may be present to such a maximum extent as to result in an extreme degree of dysphagia and obstruction, with consequent marked weight loss and malnutrition. Moersch and Judd's[9] series of cases had an average preoperative duration of symptoms of 6.1 years.

Typical symptoms are dysphagia, regurgitation of food, irritable cough and occasional hoarseness from laryngeal irritation. The patient and others are often conscious of a loud, gurgling noise whenever he swallows, which is due to the mixing of air with the contents of the diverticulum. Increased salivation is an almost constant symptom. In large diverticula the patient may be conscious of a sense of pressure in the left side of his neck that increases on swallowing. A foul breath due to food retained in the diverticulum is often noticed by the patient.

Spillage and overflow from the sac constitute a definite hazard. Deaths from lung abscess and pneumonia have been reported as a direct result of emptying of the contents of the sac into the tracheobronchial tree when the patient was asleep or inebriated.

Diagnosis

The diagnosis is suggested by the patient's history and symptoms and is easily confirmed by x-ray examination. A positive diagnostic sign may be elicited by asking the patient to swallow rapidly two or three times and then pressing quickly over the diverticulum. This is accompanied by a peculiar squeaking and gurgling sound, which is due to the air's being forced under pressure out of the diverticulum into the pharynx. It is important to examine the esophagus in its entire length under fluoroscopy in the upright position in order to rule out additional diverticula or cardiospasm. Endoscopic examination of the diverticulum should be done routinely and is mandatory if there is any irregularity in the contour of the sac that might be suggestive of a malignant change.

Treatment

Operation is the treatment of choice. The danger of operation lies chiefly in the development of post-operative infection, as the diverticulum lies between the pretracheal fascia in front and the prevertebral fascia behind and any spillage thus has direct access to the mediastinum. Because of the danger of spillage and its subsequent infection and mediastinitis, the two-stage operation has become the procedure of choice for the majority of surgeons who occasionally perform such an operation.

The method of operation by inversion is attended by little or no danger of sepsis, since the sac is not opened, and if the dissection has been accurate and the closure correct the results are universally good.

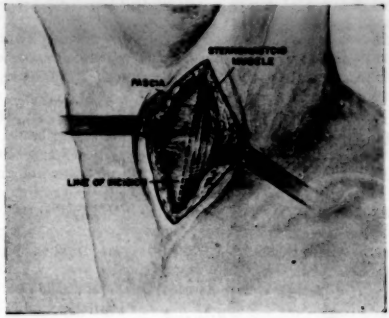

FIGURE 2.

The method is not applicable to the rarely observed large diverticulum or to those diverticula in which there is any suggestion of malignancy. Many large diverticula, however, become quite small once their overlying fascia has been removed, and may easily be treated by invagination.

Anesthesia is carried out by means of combined local infiltration and transcervical block. Thus the patient is conscious and has an active swallowing reflex, which is often of considerable help in both identifying the sac and completing its dissection. A Levine tube is always passed to the stomach prior to the operation.

Figure 2 shows the first step in the operation. The left side of the neck is illustrated, as the diverticulum more frequently presents on this side. An incision about five inches in length is made along the anterior border of the sternomastoid muscle, from just above the sternal notch, upward and outward.

The skin flaps are reflected and a vertical incision made through the deep fascia anterior to the sternomastoid muscle. The omohyoid muscle is exposed and sacrificed. The dissection is then developed to expose the carotid sheath, which is protected and retracted laterally. The left lobe of the thyroid gland is freed from its overlying fascia.

The middle thyroid vein is ligated, and the left lobe of the thyroid gland is rotated upward and retracted anteriorly. The recurrent laryngeal nerve is exposed at this point in the dissection and must be carefully protected. The superior thyroid vessels are then ligated and divided, and the entire left lobe of the thyroid gland is rotated medially and downward (Fig. 3).

We have not made it a routine practice to ligate the inferior thyroid vessels, as we have found that we obtain what we consider better exposure by

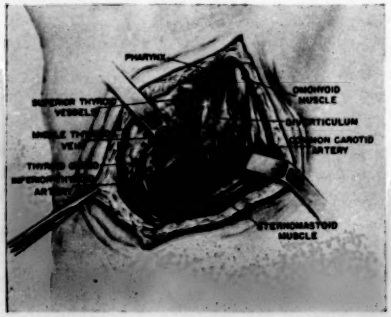

FIGURE 3.

ligation of the superior thyroid vessels. This allows an excellent exposure of the entire esophagopharyngeal area, and the diverticulum is usually readily visible. It presents as a small, redundant fold of mucosa protruding just behind the lobe of the thyroid gland. If the patient is conscious and is asked to swallow, the diverticulum readily bulges up into the wound. If at this point the diverticulum is found to contain food or fluid, the sac must be emptied by the anesthetist before proceeding further.

The fascia overlying the diverticulum is then removed. The sac is carefully grasped with fine smooth forceps and dissected free from the esophagus by gentle pledget dissection. Great care must be taken not to grasp the sac at any time during the procedure with any pointed forceps or crushing instrument. As the dissection progresses, it will be found that the diverticulum is covered with a thin layer of fascia that can readily be removed under traction, by gentle dissection.

In Figure 4 the diverticulum is being drawn up into the wound, while the fascia overlying the diverticulum is being dissected downward around the neck of the sac. An almost constant finding in all our cases has been a small plexus of veins at the

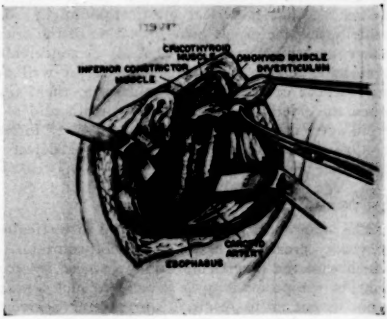

FIGURE 4.

superior border of the neck of the sac. These veins have proved to be a troublesome source of bleeding in this area if they are not ligated early.

The fascia is carefully dissected off the entire sac, with the result that the diverticulum then consists

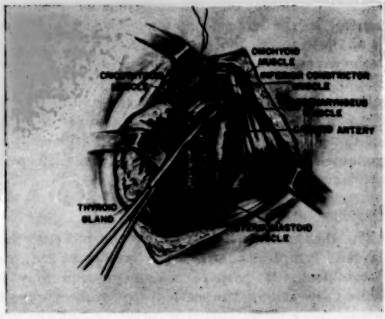

FIGURE 5.

of mucosa and submucosa only. At this point a seemingly large diverticulum will often have contracted to approximately one third its former size. It is very important that the neck of the sac be widely mobilized at its junction with the esophagus,

in order not to leave a redundant angle at the inferior border that might serve as a nidus for another diverticulum.

With the sac completely freed, the opening between the constrictor fibers becomes very well defined, and the sac may easily be invaginated into the pharynx between the inferior border of the constrictor and the cricopharyngeus.

With the invaginated diverticulum held in the pharynx, pointing downward, the fascia surrounding the neck of the sac is carefully closed with an interrupted 4-0 silk suture, after which the fibers of the constrictor are carefully sutured to the cricopharyngeus with 4-0 silk. The mucous membrane must not be penetrated in the process of completing the closure (Fig. 5).

This closure is further reinforced with a layer of fascia, which in turn is anchored to the fascia overlying the mesial aspect of the carotid sheath so that all dead space is carefully obliterated. Since the diverticulum has not been opened, there is no need of drainage.

In completing the procedure, the thyroid gland is returned to its normal position; the fascia is closed with 4-0 silk and the skin closed with skin clips.

After operation, the Levine tube is left in place for forty-eight hours. During this time the patient is given no liquids by mouth but is allowed to swallow his saliva, and fluids are given through the Levine tube and intravenously. In our experience patients have had no postoperative discomfort from the invaginated diverticulum and after forty-eight hours have been able to eat and swallow with ease.

Viewed through a laryngoscope at this time, the invaginated diverticulum appears as a redundant fold of mucous membrane lying on the posterior pharyngeal wall. At the end of six weeks the fold is further reduced in size, but it is still apparent on x-ray examination. At the end of one year it appears as a slight ridge on the posterior aspect of the pharynx and unless looked for would not be seen.

Case Reports

Case 1. A 56-year-old edentulous man had symptoms of dysphagia and fullness in the throat after eating, accompanied by a more or less chronic cough for a period of 3 months. He was treated by operation by invagination and discharged on the 6th postoperative day. X-ray examination at the end of a year showed the esophageal mucosa in the region of the diverticulum to be smooth. The patient has been completely asymptomatic since the operation.

Case 2. L. M., a 72-year-old edentulous man, had observed increased salivation for over a year and a sensation of food stopping in his throat, accompanied by gurgling noises while eating. The patient also had a chronic cough and had noticed that the breath was foul. Operation by invagination was performed. He was discharged on the 6th postoperative day.

Films of the esophagus taken nine months after operation showed some thickening of the mucosal folds in the region of the diverticulum; the esophagus was otherwise completely normal. The patient has been asymptomatic since the operation.

Case 3. O. R., a 57-year-old man, complained of a chronic cough for two years, accompanied by frequent choking sensations after eating. Coughing spells were occasionally accompanied by the regurgitation of undigested food particles. He also had a sensation of food sticking in his throat and increased salivation. All these symptoms were more acute when he was lying down and thus made it difficult to sleep. Operation by invagination was performed. The patient was discharged on the 5th postoperative day.

Barium examination of the esophagus made approximately five months after the operation showed the esophageal mucosa to be smooth with no evidence of the diverticulum. The patient has been completely asymptomatic since the operation.

Case 4. R. M., a 45-year-old man, complained of slight dysphagia and regurgitation of food accompanied by a feeling of fullness in the throat of one month's duration. Operation by invagination was performed. The patient was discharged on the 5th postoperative day.

Barium examination of the esophagus, made approximately sixteen months after the operation, showed the diverticulum to have completely disappeared. The patient has been asymptomatic since the operation.

Conclusions

An esophageal diverticulum is a true herniation of the mucous membrane of the esophagus through the posterior wall of the pharynx. Its formation and development depend on a pre-existing defect in the posterior pharyngeal wall and inco-ordination of the cricopharyngeal pinchcock. Contributing factors are the patient's age and eating habits.

The procedure of inverting the diverticulum into the pharynx is offered as a valuable addition to the armamentarium of methods of dealing with this condition.

It is especially applicable to cases in which the patient is considered a poor risk and for use by the general surgeon who may occasionally treat such a case. It completely eliminates the complications that may arise from an open esophagus.

122 Railroad Street

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INTRAVENOUSLY ADMINISTERED ACTH*

A Preliminary Report

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BOSTON

SAYERS and his co-workers[1] demonstrated that large doses of ACTH administered intravenously over one half hour disappeared rapidly from the blood stream in two normal subjects, while giving rise to maximum but transient adrenal cortical stimulation. Gordon[2] first drew attention to the fact that the administration of ACTH in a *continuous intravenous drip* led to sustained adrenal cortical stimulation in human subjects, and he emphasized that relatively small quantities of ACTH were required. This was identical with the experience of Ingle,[3] who was able to produce greatly enlarged adrenal cortices in rats given small quantities of ACTH over a number of days by a continuous intravenous infusion. These findings all suggested that the intravenous infusion of a small but constant quantity of ACTH over a prolonged period of time afforded optimum adrenal cortical stimulation. The fact that the increasing shortage in the supply of cortisone is drawing ever more heavily on the available supply of ACTH leads us to publish this description of our preliminary experience with the intravenous method of ACTH administration in about 100 subjects, since it is efficient and effective in the treatment of hospitalized patients.

TABLE 1. *Relation of Duration of an Intravenous Infusion of ACTH to Effect on Adrenal Cortical Activation.*

DOSE OF ACTH	DURATION OF INFUSION	DURATION OF EOSINOPENIA	17-KETOSTEROID EXCRETION
mg.			mg./24 hr.
20	1 min.	0	6.9
20	4 hr.	10 hr.	15.3
20	8 hr.	18 hr.	18.5
20	16 hr.	36 hr.	24.0
20	24 hr.	48 hr.	30.0
20	48 hr.	72 hr.	29.1 (1st 24h) 34.5 (2nd 24h)

Methods and Material

The experimental work was carried out on the metabolic and medical wards of the Peter Bent Brigham Hospital. ACTH (Armour) was dissolved in 500 ml. of saline solution or a 5 per cent solution of dextrose in water and infused intravenously over a period of eight hours. The use of a 25-gauge ½-inch long hypodermic needle, inserted in a superficial arm vein and tightly taped down, allowed the patient mobility and prevented irritation of the vein over prolonged periods of infusion. Eosinophil counts, 17-ketosteroid determinations and chemical procedures were studied by methods previously described. The fall in circulating eosinophils[4] was followed as a *qualitative* measure of adrenal cortical activation, and the rise in urinary 17-ketosteroid excretion during the day of the infusion[5] was used as a *quantitative* measure of the adrenal cortical response.

Relation Between Duration of Administration of a Given Dose of ACTH and Response Obtained

The administration of 20 mg. of ACTH in one minute did not lead to any measurable adrenal cortical activation, as was shown by the complete absence of a fall in circulating eosinophils over a period of six hours (Table 1). However, the same dose (20 mg.), when given over an eight-hour period, produced a marked adrenal response. This was evidenced in 10 subjects by a mean fall in eosinophils of 62 per cent in four hours, 96 per cent in eight hours and 98 per cent in twelve hours and by an average increase in the twenty-four-hour excretion of 17-ketosteroids of 10.8 mg. (range 3.4 to 22.0) on the day of the infusion. These changes did not occur in patients with severe Addison's disease or in patients who had undergone complete bilateral adrenalectomy[6] (Table 2). This procedure thus constitutes a reliable test for adrenal cortical reserve.

TABLE 2. *Changes in Circulating Eosinophils following the Intravenous Infusion of 20 mg. of ACTH over a Period of Eight Hours.*

NO. OF PATIENTS	GROUP	FALL IN EOSINOPHILS AT 4h AVERAGE RANGE		FALL IN EOSINOPHILS AT 8–12h AVERAGE RANGE	
		%	%	%	%
10	Normal subjects	62	33–96	98	91–100
5	Patients with Addison's disease	13	0–42	0	0
5	Hypertensive patients previously subjected to bilateral complete adrenalectomy	8	0–18	3	0–8

*From the Medical Clinics, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.
This study was aided in part by grants from the National Institutes of Health, U. S. Public Health Service, and the Armour Laboratories, Chicago, Illinois.

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In one subject in whom the same dose of 20 mg. was given over even longer periods, it was found that this quantity still resulted in full stimulation of the adrenal cortex when the injection period was increased to forty-eight hours (Table 1). It is therefore quite evident that the duration of intravenous infusion is an important factor in the magnitude of the response of the adrenal cortex to a standard quantity of ACTH.

From the results obtained, it appeared that an eight-hour intravenous administration of ACTH stimulates the adrenal cortex for sixteen to twenty hours, thus approximately meeting a patient's requirements for the day. Since this seemed to be a practical period of administration, it was chosen for therapy. When 20 mg. of ACTH was given *daily* to a subject with normal adrenal glands, a maximum response was attained in from three to eight days, after which the degree of activation remained approximately the same with repeated infusions at the same dose level (Table 3). Thus, by means of

TABLE 3. *Cumulative Adrenocortical Activation Following the Daily Infusion of 20 mg. of ACTH over Eight Hours.*

DAY	DOSE	THERAPY	NO. OF EOSINOPHILS PER CU. MM.		17-KETOSTEROIDS EXCRETION
	mg.		0 hr.	10 hr.	mg./24 hr.
1	0		126	—	6.9
2	20	ACTH given intravenously	130	0	14.9
3	20	ACTH given intravenously	266	0	23.6
4	20	ACTH given intravenously	135	0	20.3
5	20	ACTH given intravenously	300	6	22.1

intermittent administration of ACTH for eight hours of each twenty-four hours, excessive stimulation of the adrenal cortex and the formation of excessively large adrenal cortices was apparently avoided.

Relation Between Dosage and Response

With the duration of infusion constant at eight hours, it was established that adrenal cortical stimulation increased approximately linearly with the dose of ACTH up to 10 to 20 mg. Larger doses did not appear to increase adrenal cortical activation any further (Table 4) once this maximum was reached. The adrenal cortical stimulation obtained by an eight-hour infusion of 20 mg. of ACTH was found to be comparable to that obtained by the intramuscular injection of from five to ten times the intravenous dose injected at six-hour intervals throughout the twenty-four hours.

Clinical Application of Intravenous Administration of ACTH

To date ACTH has been infused in over 100 patients or normal subjects. No anaphylactic reactions have been noted, either during or after the infusion. However, until a much larger group has been studied, patients should be watched for the first thirty minutes of the infusion for any evidence of anaphylaxis. The longest follow-up period is five months at the time of writing, and as many as 32 infusions have been given to the same patient over a period of sixteen weeks without evidence of sensitivity reactions or of decreased activation of the adrenals. Patients given an intravenous infusion thirty days after the end of a series of intravenous treatments showed a normal response, without any untoward reactions. It should be

TABLE 4. *Adrenocortical Response to Increasing Doses of ACTH Infused Intravenously over a Period of Eight Hours.*

ACTH DOSE mg. equiv. to LA-1-A	17-KETOSTEROID EXCRETION DURING 24-HOUR PERIOD (INCLUDING INFUSION) TOTAL mg./24 hr.	INCREASE mg./24 hr.
Control	15.4	—
1.0	18.2	2.8
2.5	21.6	6.2
5.0	26.3	10.9
10.0	28.6	13.2
20.0	28.9	13.5
40.0	28.4	13.0

stressed, however, that the period of observation in this series is at present too short to warrant a conclusive answer to the question whether or not drug resistance or unpleasant allergic phenomena might occasionally develop after longer intervals have elapsed.

It is of interest that intravenously administered ACTH resulted in a normal adrenal response in 4 patients who had become unresponsive to the same preparation of ACTH injected intramuscularly. That a tissue factor is responsible for the destruction of ACTH in such instances is further

TABLE 5. *Eosinophil Response to Intravenous Infusion of ACTH over Eight Hours on Consecutive Days, both before and after a Period of Oral Administration of Cortisone.*

DAYS	DOSE OF ACTH	MAXIMUM EOSINOPHIL FALL
	mg.	%
1	12	98
2	12	99
3–23	7500 mg. cortisone acetate by mouth over a period of 20 days	
24	20	0
25	20	49
26	20	97
27	20	100

suggested by the fact that the intramuscular administration of a similar dose of ACTH as a constant drip, comparable in dose and time to that given intravenously, failed to result in any fall in the eosinophils in one such unresponsive patient.

Intravenously administered ACTH may also prove helpful in overcoming the functional involution of the adrenal cortex that follows prolonged cortisone therapy.[7, 8] An example is shown in Table 5. It appears that reactivation of the adrenal

cortex is achieved somewhat more rapidly by the intravenous than by the intramuscular administration of ACTH — and with a very much smaller quantity of ACTH.

Clinical Results

Twelve representative cases are described:

Six patients with rheumatoid arthritis were given ACTH intravenously for twelve to nineteen consecutive days, and satisfactory remissions were obtained. It is not possible to say as yet whether the permanent results are in any way different from those obtained with large doses of intramuscularly administered ACTH. It does appear, however, that full subjective improvement is obtained somewhat earlier in the course of therapy, usually on the second or third day and with approximately 1/5 to 1/10 of the intramuscular dose of ACTH.

In one case of exfoliative psoriasis resistant to intramuscular ACTH, marked clearing of all skin symptoms was obtained within seven days with daily intravenous administration of 20 mg. of ACTH. One patient with acute exfoliative dermatitis following the use of penicillin ointment showed complete clearing of her skin after five days of daily intravenous administration of 20 mg. of ACTH.

One patient was given 20 mg. of ACTH intravenously during an acute attack of gout with immediate decrease of pain and other inflammatory symptoms.

One patient with generalized Boeck's sarcoid involving lungs, lymph nodes, skin, muscles and the uveal tract, who had been admitted primarily because of steadily decreasing pulmonary reserve, was given ACTH intravenously (20 mg. daily) for fifteen days. Pulmonary-function studies obtained before and after ten days of therapy showed an increase in vital capacity from 850 ml. to 2450 ml., in maximal breathing capacity from 30 to 71 liters and in arterial oxygen saturation from 88 per cent to 96 per cent on the tenth day.* X-ray examination further showed considerable clearing of the diffuse pulmonary infiltration and a moderate decrease in the size of the hilar nodes.

One patient with ulcerative colitis and rheumatoid arthritis showed improvement in both conditions during a ten-day course of intravenously administered ACTH (20 mg. daily).

One patient with nephrotic edema (the nephrotic stage of glomerulonephritis), resistant to ACTH given intramuscularly (160 mg. daily), was given the drug intravenously (20 mg. daily) for six days. A definite fluid retention with weight gain was observed during the period of administration of ACTH and a satisfactory diuresis occurred on the fourth day after it was discontinued.

*We are indebted to Drs. John W. Woodbury and C. Sidney Burwell for these studies.

From preliminary experiences as illustrated, it appears that the clinical results obtained with intravenously administered ACTH (20 mg. daily) are quite comparable to those obtained with doses of five to ten times this amount of the same material given intramuscularly.

Summary and Conclusions

The effectiveness of ACTH given by constant intravenous drip in man, as first shown by Gordon,[2] has been fully confirmed. Whereas 20 mg. given intravenously over a one-minute period shows no significant adrenal cortical activation, the same amount given over a period of two days will triple the daily 17-ketosteroid excretion. Over an eight-hour period, 20 mg. of ACTH affords the maximum adrenal cortical stimulation in the average individual; hence nothing is gained by increasing the amount of ACTH administered at one time. However, prolonging the duration of the infusion increases the adrenal cortical response to a given dose of ACTH. In addition to representing a substantial saving in material and cost of therapy, the intravenous route activates the adrenal gland in patients unresponsive to intramuscularly administered ACTH and is capable of reactivating the adrenal cortex suppressed by cortisone therapy after two to three days. The infusion of 20 mg. of ACTH over an 8-hour period in conjunction with determination of the 0 and ten-hour eosinophil count constitutes a standardized test for adrenal cortical reserve. No instances of anaphylactic reactions have been observed. The side-effects are analogous to those observed with intramuscularly administered ACTH or cortisone. The intravenous infusion of ACTH is economical and, provided that the patient is kept under observation during the early part of the infusion, may be considered safe.

We are much indebted to Mr. Roy Amicangioli, whose unfailing co-operation allowed us to work out the fundamentals of intravenous administration of ACTH.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SCIENCE: SURGERY

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ACCORDING to Whitehead, man's faith in a rapid and conscious development of technology was a product of the nineteenth century. He considered this faith sufficiently peculiar to that century to distinguish it from all preceding ones. This same philosopher also viewed the last twenty years of the nineteenth century as one of the "dullest stages of thought since the time of the First Crusade." "The period," he stated, "was efficient, dull, and half-hearted. It celebrated the triumph of the professional man."

It happens that what is commonly referred to as "modern" surgery came into being during these twenty years, for these were the years that immediately followed the discovery of asepsis. So much of contemporary surgical activity is a continuation and projection of the great development of technology that took place during the closing decades of the nineteenth century that it is necessary to sift the trends of the past fifty years with care in order to identify the outlines of a new surgery. These outlines are even yet indistinct in some quarters, but it is believed that they represent twentieth-century, or truly "modern," surgery. This new surgery has been described in many different ways, but for the present purpose emphasis will be placed on two features that serve to distinguish it from what will be called nineteenth-century surgery, in which attention was concentrated on the technology of the operation. The first of these two features is a lifting of the eyes from the local lesion and the operation designed to deal with it to regard the more general aspects of surgical disorders; the second, the introduction of the methods of experimental science as aids to the solution of clinical problems.

Nineteenth-Century Background

The surgeon was not alone in bringing his attention to focus on the local manifestations of disease. All medicine followed the same course. It is customary to turn back to Morgagni in the mid-eighteenth century for the origin of the concept that certain diseases are localized. This concept was of tremendous importance to the surgeon, for when confronted by humoral or generalized disorders he found no place for his handicraft. Flatulence, costiveness, dyspepsia, plethora or dyspnea as general disorders meant little to the surgeon. They were treated with purgatives, bloodletting, alteratives or magistrals. Once a disease was localized to an organ, however, the surgeon could sharpen his tools and go to work. Gallstones, cancer of the colon, gastric ulcer or stenosis of a bronchus offered a specific and direct surgical challenge.

During the nineteenth century all of medicine was swept along in the search for the location of disease processes. Morgagni had traced certain diseases to individual organs of the body. Bichat (1771–1802) carried the same concept to tissues, and finally Virchow (1812–1902) established pathology on a cellular basis. This trend in the localization of disease to small and still smaller structural units paralleled what Whitehead has called the notion of *atomicity*, which pervaded nineteenth-century science. It was introduced into chemistry by John Dalton. Schleiden (1838) and Schwann (1839) established the cell as the structural unit for biology in general. The culmination of atomicity in the biologic area was of course the work of Pasteur, demonstrating the fact that minute living organisms are capable of inducing disease at the cellular level and with specific pathogenic effects.

Events in clinical medicine and surgery closely followed the direction of the Morgagni–Bichat–Virchow axis. The effect is observable in the early decades of the nineteenth century. Thus, Laennec started his treatise on auscultation with the statement: "Of all the diseases which are essentially local, those of the thoracic organs are unquestionably the most frequent." And of course his stethoscope is an early example of the technical aids to the diagnosis of localized disease in the living subject that were to be multiplied throughout the century and finally crowned in the closing decade by the discovery of the x-ray.

It will be instructive to pause and acquaint ourselves with the outlook of a surgeon of the early nineteenth century before he was caught up and molded by the events that were to overtake him. His viewpoint was quite different from that of his counterpart at the close of the century. In fact, this early nineteenth-century surgeon appears to have more in common with the surgeon who will be identified as representative of the mid-twentieth century than with those who came between. As an example of his outlook, consider the following paragraph from the treatise of Abernethy, "On the Constitutional Origin and Treatment of Local Disease" (1817 edition):

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> An evil seems to me to have arisen from the artificial division of the healing art into the medical and surgical departments. This division has caused the attention of the physician and the surgeon to be too exclusively directed to those diseases, which custom has arbitrarily allotted to their care. *The effects of local disorders upon the constitution* have, in consequence, been too little attended to; and indeed I know of no book, to which I can refer a surgical student for a satisfactory account of those febrile and nervous affections which local disease produces, except that of Mr. Hunter. *The reciprocal operation of constitutional disorders upon local diseases* has obtained still less attention. [Author's italics.]

The return to this position may be observed in many places today, a century and a half later. Surgeons and physicians are united in close teamwork, studying the constitutional problems of their patients, assaying the functions of the endocrine organs, exploring psychosomatic afflictions, conferring about nutrition, fluid balance or renal function or pursuing any one of a number of similar subjects in which local and constitutional aspects may be jointly appraised.

In the intervening years, however, the surgeon, as the person best qualified to undertake an urgent mission, was obliged to busy himself with other things. Two revolutionary discoveries, one made in 1846 and the other in 1867, suddenly made him the key figure in a great technologic development of the healing art. These discoveries were, of course, anesthesia and asepsis. Anesthesia made it feasible to deal with localized disease without causing pain. Asepsis made it possible to dissect living tissues and reach sites of localized disease without introducing the hazard of infection, which carried greater immediate risk than the lesion itself. Anesthesia and asepsis were such momentous discoveries that they established a new base-line, not only in surgery but throughout biology and medicine as a whole. As one looks backward, the brilliance of the nineteenth-century revolution that was based on these discoveries obscures all lesser milestones. This revolution is pointed to with pride as having given birth to the modern surgeon. Actually, it nearly did him in, for it saddled him with a technologic burden that was crushing in its weight and under which he is still forced to stagger.

The years 1875–1900 saw the invention of a vast number of technologic procedures that comprise a large portion of what is recognized as operative surgery. A major number of the operations that appear on operating schedules today were envisioned and carried out during the closing decades of the nineteenth century. It is true that the technics have since been modified and perfected and that the fields of application have been both widened and made more precise.

The rise of the great technology of surgery certainly fulfilled a mighty humanitarian purpose. In addition, it was by no means barren of scientific import. Surgical technics have enriched all biological science. They enabled Pavlov to construct his gastric pouch, Sherrington to explore the nervous system and Eck to construct his fistula — to mention but a few examples. But the surgeon as an inventor of operations has been forced to remain at his post on the production line. There could be no industry as such, to which patent rights might be assigned and the problems of production delegated. The indeterminable variables that make each case a problem unto itself continue to make surgery a practical art rather than an applied science.

In addition to the contribution of technics to experimental science, the continued exercise of these technics on the human body clarified and established the nature of internal disease by bringing it to light in the living patient. This was the major contribution of nineteenth-century surgical endeavor to medicine as a whole. A quickening in the understanding of disease came through the impetus afforded to pathology. Before this time a gap had existed between an external pathology (ulcers, tumors, gangrene and so forth) regarded as the sphere of the surgeon and internal pathology disclosed only at autopsy and held to be within the province of the internist. With access to the internal organs during life came a medicochirurgical pathology. The internist and the surgeon met in common concern to discuss cholecystitis, appendicitis, pancreatitis and many other diseases previously little known. The proper timing of therapeutic intervention became a subject of vigorous and at times bitter debate, in which the surgeon was usually found pleading for prompt action as opposed to dilatory contemplation.

To accept contemporary surgery as merely a continuing exploitation of anesthesia and asepsis would be to focus entirely on the tidal wave of technologic development and the by-products that have been described. However fruitful this phase of surgery has been, it does not represent the unique content of the twentieth-century surgery that is our given task to explore. Before a new phase is considered, however, the technologic development will be followed into the present century.

Projection of Nineteenth-Century Surgical Technology into the Twentieth Century

Most apparent to the layman, and until very recently most widely acclaimed by surgeons themselves, is the forward projection of nineteenth-century technology. Although its ramifications are infinite and its contributions to the relief of human suffering beyond measure, this aspect of surgery is so familiar that it will require no elaboration after its outlines have been defined and its characteristics identified.

The surgical agenda of the year 1900 contained at least three categories of operative procedures. First, there were the operations that had existed for centuries and that had never ceased to be practiced. Examples are: vascular ligations, amputations of extremities, the ablation of superficial tumors,

amputation of the breast, release of strangulated hernia, removal of vesical calculi, trephining and drainage of empyema. The first and most evident effect of the introduction of Listerism was a reduction in the mortality rate of these procedures from 40 to 50 per cent to 1 to 2 per cent. A second category embraced surgical procedures that had been performed from time to time but had become too dangerous in the milieu of hospital cross-infection and had largely been abandoned by the time of Lister. Some of these, such as ovariotomy, had been successfully performed in private dwelling houses prior to asepsis. Further examples were splenectomy, nephrectomy, operations for goiter, intestinal suture, the opening of joints, resection of major joints, plastic procedures, and repairs of nonstrangulated hernia. The third category included operations that were newly devised between 1875 and 1900 under the protective mantle of asepsis. Bone and joint surgery that previously had been directed toward resection or amputation now became reconstructive. Osteotomy, open suture of the patella and olecranon and the surgical ankylosis of joints were rapidly developed. Other examples included laminectomy, exploratory laparotomy with the development of visceral surgery (suture of perforated ulcer, appendectomy, gastric resection and so forth), suture of the heart, transperitoneal nephrectomy, pyelotomy, nephropexy and total hysterectomy.

In addition to modifying and perfecting the technics and sharpening the indications for the use of this abundant legacy from the preceding century, the surgeons of the twentieth century have greatly extended the scope of operative surgery. One need only mention the developments in the surgery of the central nervous system, the surgery of the thorax, and the recent spectacular development of the surgery of the heart and great vessels. Advance into these areas had been delayed for many reasons, some of which will be referred to later. From the purely technical standpoint, the surgery of the brain demanded a degree of perfection in aseptic technics and hemostasis that was only being approached at the end of the last century. Surgical conquest of the thorax required more precise delineation of localized disease than was afforded by the stethoscope of Laennec. This clearer delineation came with the refinements of roentgenography. In addition, the art of anesthesia required extension of its scope beyond simple obliteration of pain to include the maintenance of life-supporting oxygenation before the surgeon could expose and dissect the respiratory organs. From the standpoint of timing, it is appropriate that the ultimate conquest, that of the citadel of the body — the heart itself — has been accomplished within the span of the first half of the twentieth century. During the past decade this long-envisioned triumph has been achieved by the ingenious merging of technics previously developed for the vascular system and the thorax.

Technologic development during the present century not only has extended the range of operative surgery, and by so doing increased the number and complexity of technics, but also has enabled significant steps to be taken toward the simplification of older procedures. It is difficult at this time to recapture the circumstances under which such a crude device as the Murphy button was heralded as a notable invention. The many elaborate technics for carrying out a closed anastomosis of the large bowel have largely disappeared, — and not altogether because of the protection afforded by antibiotics. Such examples could be multiplied many times. The pressures to shorten the number of days required in hospital and to economize on ancillary personnel are powerful forces that have already stimulated the invention of simpler and more direct approaches. The disappearance of two-stage operations and the advent of early postoperative ambulation are significant advances in this direction.

But better care of the surgical patient during the present century has come about predominantly through fuller understanding of the implications of fluid and electrolyte balance, the need for restoration or maintenance of an effective blood volume, the control of infection by specific antibacterial agents, the importance of adequate oxygenation and safe anesthesia, the vital role of nutritional support and many other concepts that have guided treatment adjuvant to the operation itself. These advances have paralleled the development of a more precise and certain technology and have often been the determinants that made expert craftsmanship feasible.

The full account of technologic advances in surgery during the twentieth century reposes in the countless issues of periodicals and annual reviews and reports. This line of development has culminated at midcentury in such feats as the resection of a segment of the thoracic aorta for coarctation and the enlargement of stenosed valves of the heart. But if one could have shown these lesions, — or for that matter a primary carcinoma of the lung or an acoustic neuroma, — to a master surgeon of the 1890's he would have recognized immediately that a surgeon should be busying himself with them. Obviously he would not have possessed the skills to carry out the actual procedures, nor could he have envisioned the diagnostic steps that now permit precise recognition of these lesions in the living subject. But he would have been aware that the path he was following would lead inevitably to these goals. It is significant that total pneumonectomy was performed in dogs while the carbolic spray was still in use.

Twentieth-Century Surgery

It has been proposed that a characteristic feature of what can be identified as twentieth-century surgery is a return to certain broad concepts held at

the beginning of the nineteenth century, as exemplified by the concern of Abernethy about "*the effects of local disorders upon the constitution*" and "*the reciprocal operation of constitutional disorders upon local diseases.*" The significance of this viewpoint is immediately enhanced when it is conceded that *a surgical operation in itself constitutes a local disorder*, at times of the greatest magnitude.

There is a strong temptation to accuse the surgical technologist of the early decades of this century of having neglected the general condition of his patient in an intense preoccupation with operative technics. Undoubtedly this did happen and still occurs today. However, surgical technology burst on the world and developed rapidly before systematized knowledge became available for the interpretation of the many complex mechanisms and reactions that attend surgical disease and the operation itself. Until the vague and ill-defined clinical symptoms of disease could be translated into understandable biologic, chemical and physical terms, their control and management was of necessity undertaken on an experiential basis (secundum artem) or ignored altogether. The operation as a technical undertaking forged ahead of the knowledge required to guide and control its use. For this reason the operation appeared as and actually was a dangerous affair, not infrequently ending in disaster. But with all its hazards the operation was frequently the *only measure that could be undertaken* under exigent circumstances.

In order to reach the objective desired by Abernethy two things were necessary: first, an advance in the systematized knowledge within the basic sciences, and second, the introduction of the methods of experimental science into clinical surgery.

The management of intestinal obstruction is an example to the point, because the devastating and fatal alterations in the fluid and chemical balances of the body that attend this lesion are well known. Existing knowledge about intestinal obstruction was compiled in monograph form by Sir Frederick Treves at the turn of the century (1899 edition). After many pages devoted to a scholarly exposition of the anatomico-pathologic features, Treves presented its symptoms, signs and treatment. "Operation may be dangerous, and is, indeed, very dangerous, but delay is worse," he stated. "There can be no purpose in delay. The operation should be performed at the earliest possible moment."

Treves thought of fluid administration only in terms of relieving the intolerable *thirst* of his patients. "Curschmann says that thirst may be relieved by subcutaneous injections of saline solutions." "No evidence has been induced in favour of intravenous injections as a means of allaying intense thirst." The vomitus was looked upon only as "foul and decomposed contents of the disturbed bowel." "It is well that the patient should be rid of this, for the one great danger which threatens him is self-poisoning from his own bowel."

When these words were written, the concept of acid-base equilibrium was as yet not formulated and the significance of dehydration totally unappreciated. Today "rehydration" has become a household word among surgical staffs, along with "correction of the electrolyte imbalance." Even in the face of the dangerous strangulated obstruction a precious hour or so may be devoted to restoration of fluid and electrolyte loss before the direct surgical attack is launched.

The recognition of the need for an interpretation of constitutional reactions to local disorders preceded their clarification, often by many decades. The surgeon was keenly aware that he was working in the dark. The response of the body to extensive trauma troubled the wound surgeon for centuries. Even though the shattered limb was amputated and every organ of the body was presumably sound, death was likely to occur as the terminal event of a constitutional disturbance known as wound shock. "This symptom," wrote Longmore in 1895, "is generally described as the 'shock' of a gunshot wound. It may be regarded as an expression of sympathy of the whole frame with a part suddenly subjected to serious injury."

This response of the body to a wound could not be interpreted on the basis of anatomico-pathologic concepts as defined by the Morgagni-Bichat-Virchow axis. The challenge presented to the inquiring mind of the young surgeon is well described by George Crile:

> It was while serving as house officer at University Hospital [1888], when I was not yet twenty-four years of age, that I witnessed for the first time the death of a human being. The patient. . .William Lyndman, was young and strong. *Every organ of his body was sound.* He had lost but little blood, although both legs had been crushed by a streetcar. When he entered the hospital high amputations at the hip were performed. . . .
>
> I sat beside the bed of this vigorous young friend of mine studying his failing body energies. The steady increase in the pulse rate, and the decrease in the pulse pressure; the slow and gradual increase in the cold, clammy sweat; the dilated pupils; the pallor, the shrunken face; the gradual increased rate of respiration — each breath more shallow than the former — followed by fading consciousness, made. . .death. . .as inevitable and peaceful as a sunset.
>
> During my vigil throughout the night, I, a new intern without experience and never having seen a serious illness, read the various surgical opinions regarding this type of injury and the treatment recommended, making notes in my diary on the changing condition of the patient.
>
> I had carried out the treatment advocated by Gross, the greatest surgical authority of the day, but nothing had the slightest effect on the progress of death. I was overwhelmed with my lack of understanding of what was happening and baffled over the inefficiency of the treatment.
>
> . . .The next day in an abandoned shed on the grounds of the old University Hospital, I experimented on a cat, on the assumption that in traumatic shock blood accumulates in the great venous trunks, especially in the chest, and that this had caused the death by shock of William Lyndman. Inexperienced as I was, I did not realize that to solve the problem of the cause of Lyndman's death was to solve the mystery of life.
>
> . . .In a few days I asked permission to use that old shed for research to ascertain if this transfer of blood at death was a

fact, and if so, whether in any death or just in death from shock. . . . This, so far as I know, was the first time animal experiments were used to throw light on shock.

It soon occurred to me that if I could attach the carotid artery of a dog to a column of mercury in a glass tube on which there was a millimeter scale, I would be able to make blood pressure readings.

. . .Thus with very little expenditure I had a simple apparatus by which I could observe and measure accurately the blood pressure changes in anesthetized animals, traumatized to the point of death from shock. [Author's italics.]*

To retrace the steps of the surgeons and their companion physiologists through the maze of conflicting experiments and hypotheses dealing with what Mann called "the problems of shocks" would lead far afield. Suffice it to say that on the basis of observations made during World War II it can now be said with certainty that William Lyndman died because he had lost approximately one half of his normal blood volume. Also, his death was not "inevitable" and in all likelihood would have been prevented today by the administration of 2000 to 3000 cc. of whole blood before and during the operation.

While Crile was puzzling about the death of his classmate, young Harvey Cushing was challenged by the death of a patient who stopped breathing under ether anesthesia. In November, 1900, Cushing arrived in Berne to work with the famous Kocher. A place was provided for him in the Hallerianum, the physiological institute of Professor Hugo Kronecker, a pupil of Carl Ludwig. The experiment proposed was designed to determine whether compression of the brain produced dilatation or compression of the small veins and capillary vessels. A small window was placed in the skull of an animal and the intracranial pressure raised by elevating a flask of salt solution that was connected with the ventricle. (The pulley in the ceiling used to hoist the flask is still shown to visitors.) Continuous records were made of the animal's respiration and blood pressure, and it was observed that as the pressure within the cranium was increased the arterial blood pressure rose correspondingly.

Subsequently Cushing brought back to this country an early model of the Riva-Rocci sphygmomanometer. This was used to record the blood pressure of the patient during the course of neurosurgical operations, "so that," as Cushing wrote, "the procedure might be as comparable as possible to the records taken upon a kymograph during an experiment in the laboratory." Thus neurosurgery developed on the basis of the introduction of the methods of experimental science into the operating room and a careful control of the effects of local disorders on the functions of the body as a whole. The technical features of asepsis and hemostasis mentioned earlier were probably of collateral importance.

*Crile, G. W. *George Crile: An autobiography.* Edited, with sidelights, by Grace Crile. First edition. 2 vol. Philadelphia and New York: J. B. Lippincott Company, 1947. Vol. 1. Pp. 27-29.

One further example will be given. In 1918 Captain Evarts Graham was sent to an army hospital to devise means of reducing the high mortality rate encountered in the management of empyema that accompanied the pandemic of influenza. Graham saw cyanotic and breathless patients hurried to the operating room, where a segment of rib was removed and a large drainage tube inserted. It was not uncommon for a patient to die in asphyxia within a half hour after the operation. "Isn't it possible," he asked the surgeons, "that admitting air into the chest causes the patient to die? Isn't open thoracotomy being performed too early in the course of the disease?"

"No," the surgeons replied, "Look at the pus that pours out. The trouble is that the operation is being performed too late!"

Graham's subsequent confirmation of his clinical observation in the experimental laboratory and the recommendations of the Empyema Commission provided a rational foundation for the management of empyema and, of still greater consequence, guided the new thoracic surgery that was to develop rapidly after World War I.

The trend illustrated by these examples is the most significant feature of twentieth-century surgery and has rapidly been gaining headway, particularly during the past two decades. It is a trend that cultivates the discipline of the mind that is needed to complement and guide surgical technology. It is a trend that re-establishes the surgeon as a biologist and as a physician in the broad sense of one skilled in the healing art. It is a trend that breaks down the sterile isolation of the surgeon at the operating table and encourages him to travel in company with others — with the internist, the physiologist, and the chemist — in a common quest for the clarification of unsolved problems.

This twentieth-century emphasis in surgery is not in conflict with a sound and competent technology, nor is it incompatible with the maintenance of the humanitarian qualities that are treasured so highly by responsible members of a great profession. The depth of its roots in the past has been shown. Many leaders in the field of practice sensed its significance and gave it support even though their responsibilities did not permit an active participation.

"I feel that my men, although they make splendid practitioners of surgery, fail to get from me any inspiration toward so-called research work," wrote Maurice H. Richardson in 1908. "Of course we are seeking all the time — and hoping that we shall find — knowledge in the fields of practical surgery; but it seems that the coming generation needs a broader field in which to work; that the men should be more than purely clinical observers."

"If you were to ask me to recommend the best book on surgery," said John B. Murphy during one of his famous clinics in 1913,

I would say that the best surgery is a good physiology, the best you can buy. Next to that is the best pathology. These two of necessity demand a third, a text-book on anatomy.

Following out that line of thought I wish you to keep in mind all the time that surgery is drifting continually from the mechanical to applied physiology. For a time it drifted to applied pathology, then from pathology to applied physiology, with pathology and anatomy as secondary requirements. When I was a student the man who went into surgery came in through the route of the professorship of anatomy. The man who was the senior assistant in anatomy became the professor of anatomy and finally professor of surgery. We have not yet heard of the professor of physiology becoming a surgeon. The professor of physiology becomes the internist, the diagnostician, but the professor of physiology will sooner or later come into surgery as his own.

Maurice Richardson identified the new surgery as "research"; J. B. Murphy, as "applied physiology." Both were right in part, but neither grasped the full significance of what was happening. Wilfred Trotter, in his lucid style, described it clearly in 1932. He identified medicine with the practical arts, like those of the farmer, the builder or the blacksmith. An applied science, in contrast, carries on its tasks by the application of ascertained principles to particular cases. In an applied science failure can be due only to ignorance; as there are no indefinable elements, success depends on pure systematic knowledge. The general process of culture appears to be directed toward the conversion of practical arts into applied sciences. Thus the art of the mechanical engineer has been almost completely transformed; the work of the electrical engineer was an applied science from its beginning.

In medicine the bulk of activity remains without a complete and sure foundation of ascertained principles — remains a practical art. The frontier between this region of art and such ground as science has gained is the most interesting area — and one in which the methods of experimental science can be employed. Even minor problems of clinical work should, when conditions allow, be submitted to methods by which an exact decision is possible rather than be decided by vague clinical impressions, by insignificant statistics, by authority or by tradition. Trotter looks on the conquest of this frontier as a most exciting intellectual adventure for young men coming from science to clinical work. This is the "broader field" that Maurice Richardson was seeking for his men.

Trotter also gave warning that a practical art that pretends to be applied science does not thereby show itself to be progressive; it only shows itself to be quackery. "Fashion and the popular voice tend always to exaggerate the conquests of science, and to press the frontier far beyond the line of its actual advance."

Concrete examples are readily at hand to illustrate the manner in which twentieth-century surgery is setting about the task outlined by Trotter. Only one need be cited. On May 19, 1950, an Arizona ranch hand was badly burned in a gasoline fire. Reference may be made to the April 16, 1951, issue of *Life* for excellent colored photographs of the burns. The man's life undoubtedly was saved by a first-aid course of management based on the present understanding of the response of the body to the local disorder produced by flaming gasoline. This understanding is the product of many years of precise measurements and experiments made by scores of investigators. Observations made by Underhill on the victims of a theater fire in New Haven on November 27, 1921, were some of the earliest.

After twenty-four hours the Arizona rancher was transported to Phoenix. There it was decided to undertake a clinical trial of ACTH. It was claimed that it "worked." The survival time of homologous skin grafts was extended and the need for fluid therapy diminished. At any rate, the burned man recovered and now can jump across an irrigation ditch and operate a tractor. "Fashion and the popular voice" then heralded what was claimed as another conquest of science. The case report was published in the January 13, 1951, issue of the *Journal of the American Medical Association*. A large industrial company producing ACTH circulated advertising brochures and made available a motion picture that displayed the clinical course of the patient. Here and there a prominent surgeon gave ACTH to his burned patients and was "favorably impressed" with the results.

Quietly and without fanfare several groups of surgeons skilled in the methods of experimental science took this problem to their laboratories. How to treat burns is a problem of serious import to the nation at the present time. On April 12, 1951, three of these groups, from widely separated parts of the country, gave their reports before the American Surgical Association. There was no evidence, they stated, to support the claim that administration of ACTH altered the survival of homologous skin grafts either in human patients or in animals. There was no evidence that the physiologic need for immediate plasma, colloid, electrolyte and water therapy in burned patients was in any way changed by giving ACTH.

Surgery as a practical art had no way of meeting this problem except by a long period of debate on the basis of "vague clinical impressions" and "insignificant statistics." A practical art can distinguish between a sound advance and a retrograde step only by the test of experience. It might have taken years of clinical trial to arrive at a sound decision. Such a course not only would have piled up a pharmacy bill of many millions of dollars but might well have cost the lives of a number of severely burned patients. A prompt and decisive answer came through submitting the question to the only methods that could provide it. And so a fully mobilized twentieth-century surgery was able to scoop *Life* by the narrow margin of four days.

It would be rash indeed to hazard a guess concerning the future course of what has been identified as

a significant trend in the surgery of the present century. It is a fragile bloom at best, developed and nourished within the sanctuary of universities and teaching hospitals, and the pattern of surgery, as well as that of medicine as a whole, is so likely to be shaped by the needs and moods of the society it serves. Indeed, Sir Clifford Allbutt, in his study of historical relations, decided that "The division of medicine into medicine and surgery had its root not in nature, nor even in natural artifice, but in clerical, feudal and humanistic conceits."

In the giant tug-of-war that is going on between science and disease the surgeon can be proud of his historical position of anchor man with both feet planted firmly in the earth. There are already indications that with the fading of the influence of the Morgagni–Bichat–Virchow axis another cycle of generalized or humoral conceptual systems of disease has been launched. The antecedents of such a movement lie in endocrinology, in psychosomatic medicine, in the hypotheses that are interwoven with the facts of intermediary metabolism. Once again medicine may be exposed to the temptations of metaphysical speculation, to the fallacies of reasoning away from the facts. If the mid-twentieth-century surgeon is forced to make a choice, let it be a return to the unadorned practical art, rather than to the pretentious medieval College of St. Côme. As anchor man it is the task of the surgeon to remain where he constantly sees and touches disease — where he is ever in contact with the troublesome facts of nature.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 37211

PRESENTATION OF CASE

First admission. A sixty-four-year-old woman entered the hospital because of failing sight in the left eye of three years' duration. Physical examination was negative except for an immature cataract of the left eye. The blood pressure was 130 systolic, 75 diastolic. Urinalysis was negative. On the second hospital day an iridotomy was performed, with extraction of the left lens. The patient made an uneventful recovery and was discharged on the sixth postoperative day.

Second admission (nine years later). The patient again entered the hospital because of severe crushing precordial pain, that radiated through to the back, coming on shortly after lunch. For about four years preceding admission the patient had episodes of exertional dyspnea and precordial pain that were relieved by rest. The character of the pain at the time of examination was similar in quality to but of far more severe intensity than the previous attacks. The pain was accompanied by nausea. It did not extend to the abdomen or legs.

Physical examination revealed a pale, apprehensive woman with a fibrillating enlarged heart beating at a rate of 120 at the apex. The blood pressure was 120 systolic, 70 diastolic.

The urine was normal. Examination of the blood disclosed a hemoglobin of 14.0 gm. and a white-cell count of 15,800, with 89 per cent neutrophils, 6 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. An x-ray film of the chest showed a tortuous calcified aorta and clear lung fields. An electrocardiogram showed an auricular fibrillation at an average rate of 90; the Q waves were small in Lead 1 and deep in Lead 3; the ST segment was elevated in Leads 2 and 3 and depressed in Leads CF_2, CF_4 and CF_8 and the T waves inverted in Lead 1 and upright in Leads 2 and 3.

The patient was put on digitalis and the usual supportive therapy and was discharged without symptoms seven weeks later.

Final admission (six years later). Three weeks before entry the patient experienced severe aching discomfort in the left leg, which when examined by her physician was felt to be colder than the right. This was considered to be due to an arterial embolus, and the patient was placed on bed rest, dicumarol and aspirin. The leg gradually became asymptomatic over a period of three days. Four days before entry she developed transient bilateral deafness, which cleared spontaneously. Four hours before admission she had a sudden severe epigastric nonpleuritic pain, which radiated around the chest to the back and toward the left shoulder. This was accompanied by some shortness of breath and sweating. Demerol was given without adequate relief, but a subsequent injection of 15 mg. of morphine obtunded the pain. Shortly after this an unremarkable stool was passed.

Physical examination revealed a warm, mentally alert woman. The left eye evidenced a previous

cataract operation; the right pupil reacted to light and on accommodation. The neck veins were flat. The chest was clear to percussion and demonstrated only a few moist rales at either lung base posteriorly. The left cardiac border was 8.5 cm. from the midsternal line. The pulmonic second sound was greater than the aortic. Grade II systolic murmurs were heard at the base and apex. Auricular fibrillation was detected with a fairly regular rate of 75. No rub was heard. The liver and spleen were not palpable, nor were any abdominal masses felt. There was no costovertebral-angle tenderness. Normal peristaltic sounds were heard. Both legs were warm and free from edema and had equal dorsalis pedis pulses. Neurologic examination was normal except for questionable Babinski reactions.

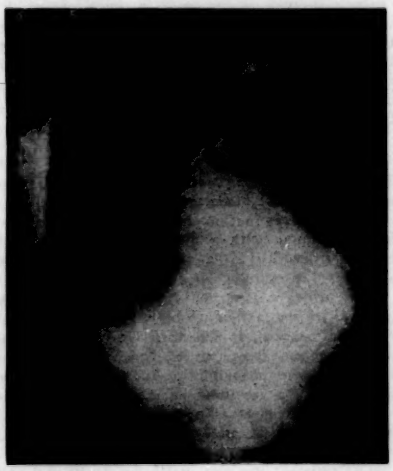

FIGURE 1. *Anteroposterior X-ray Film of Chest. Arrows point to the soft-tissue density of the aortic arch extending beyond the calcification of the intima.*

The temperature was 98.7°F., the pulse 24. The blood pressure was 150 systolic, 70 diastolic.

An amber acid urine had a specific gravity of 1.021 and gave a + test for albumin and a negative sugar reaction; the sediment contained rare white cells per high-power field. Blood studies disclosed a hemoglobin of 13.0 gm. and a white-cell count of 12,700, with a normal differential. The blood Hinton test was negative. The prothrombin time was 21 seconds (normal 17 seconds). The nonprotein nitrogen was 24 mg., the van den Bergh 0.4 mg. direct and 0.4 mg. total and the amylase 25 units per 100 cc. An x-ray film of the chest demonstrated a patch of increased density in the left base, a small amount of fluid in the left costophrenic sinus and an obscured left leaf of the diaphragm. The heart, lying in a somewhat transverse position, was prominent in the region of the left ventricle. A widened, elongated, tortuous aortic arch showed a ring of calcification (Fig. 1 and 2). An electrocardiogram was interpreted as auricular fibrillation at an average rate of 85 with a normal axis. The Q waves were of moderate size in Lead 3 and small in Lead AVF; the ST segments depressed in Leads 1, 2, AVF, V_5, V_6 and V_8; and the T waves upright in Leads V_1 and V_2, inverted in Leads 1, 2, 3, AVF, V_5, V_6, V_8 and V_9 and flat in Lead AVL.

In the hospital the patient was placed on bed rest and was followed by serial electrocardiograms. The morning after entry she felt much better because the pain had subsided, but the temperature rose to 100°F. although the pulse and respirations remained constant. The blood pressure was noted to be 200 systolic, 80 diastolic. On examination there was a slight cervical venous pulsation, a grossly irregular heart rate and a palpable liver margin 1 fingerbreadth below the costal edge. The legs were warm and both dorsalis pedis arteries pulsated. Early the following morning the patient was again

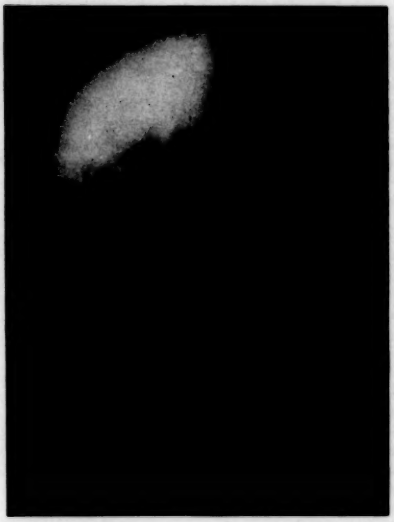

FIGURE 2. *Lateral Film of Chest.*

seized with epigastric pain of about one hour's duration that radiated to the back and spontaneously disappeared. On this day the patient had extreme hypersensitivity to touch over the thorax posteriorly on both sides. The electrocardiogram taken on the day after this episode was without significant change from the admission tracings. Four days later pain in the epigastrium and back was again noted and was relieved by holding the abdomen. The pulsatile abdominal aorta could easily be palpated, and to one examiner it was thought to be widened. Pressure on the aorta caused pain in the back. On the following day severe pain in the substernal region accompanied by a cold sweat lasted about four hours, subsided for twelve hours and recurred, radiating through to the back. Morphine was given for relief. The patient died one hour after the last attack.

Differential Diagnosis

Dr. Alfred Kranes*: May I ask whether this patient had been receiving digitalis prior to the final admission?

Dr. Conger Willliams: She was receiving it regularly.

Dr. Kranes: So some of the changes in the electrocardiogram may be interpreted as digitalis effect.

The illness for which the patient entered at the age of seventy-three years — her second admission — seems like a straightforward myocardial infarct. Certainly the history was characteristic, and although nothing was said about the subsequent course of this patient in the hospital I assume that there was no untoward incident that in any way aroused question of the diagnosis of myocardial infarction. Would you agree that the report of the electrocardiogram is not characteristic of but consistent with a posterior myocardial infarction?

Dr. Williams: Subsequent electrocardiograms did show quite characteristic changes. There was no question about that.

Dr. Kranes: Although the electrocardiogram reported here was not characteristic, subsequent ones were, so I think I shall accept that diagnosis without further discussion. What I am interested in, however, is the blood pressure. The one given here was taken shortly after admission, during the acute stages of the infarction. I am wondering whether the blood pressure subsequently rose to a higher level or was maintained at a normal level.

Dr. R. W. McAllester: After the first admission she had normal blood pressures most of the time.

Dr. Kranes: That is important.

The final admission is what really concerns me here. Whenever a patient of this age dies within a short time the cause of death is most likely to be some type of vascular accident — either an occlusion or a rupture of a vessel somewhere. If my mathematics is correct, the final "admission" lasted about seven or eight days, and therefore some other type of disease must be considered. The only illness that would be worth considering, other than some type of vascular disease, is a perforation or inflammation of one of the abdominal viscera. I find little in the course of this patient's illness to substantiate anything like that. The physicians who were taking care of her apparently wondered, because of pain radiating to the left, whether pancreatitis might have been present. The serum amylase was at the upper limit of normal. I find little in the subsequent examination to sustain a diagnosis of serious intraperitoneal disease. The statement that the patient's abdominal aorta could be palpated would make me believe that her abdomen was rather soft and therefore not the site of serious intra-abdominal disease.

If this was a vascular accident, what vessel was involved and with what? Naturally one's first thought is whether she had another myocardial infarct. If it was, it was an extremely atypical one. I am inclined to believe she did not have a coronary occlusion for a number of reasons. First, the type of pain described here is not that usually encountered with coronary occlusion; it was not substernal except for the terminal episode. Secondly, it had this curiously recurrent pattern, which one does not usually see with a coronary occlusion. Neither its location nor its radiation to the back suggests myocardial infarction. To be sure, the pain during the second admission was described as radiating to the back, but the constant back pain described in the terminal admission is not characteristic of coronary disease, although it has been known to occur. Furthermore, there was a rise in the blood pressure, an uncommon phenomenon in severe myocardial infarction. And finally, there were no characteristic electrocardiographic changes. Those that were described were nonspecific; they suggest the residual effects of the previous occlusion — possibly also a digitalis effect, and perhaps a slight left-ventricular strain. Would you agree with that, Dr. Williams?

Dr. Williams: Yes; that is exactly what we thought.

Dr. Kranes: For all these reasons I do not think she had a myocardial infarction. She could have had a pulmonary infarct. It would be interesting at this point to look at the x-ray films, Dr. McCort.

Dr. James J. McCort: The films of the first and second admission are not available. The chest examination made on the third admission shows the peripheral lung fields to be clear. A small amount of fluid is present in the left pleural cavity and in the major fissure on the left side, but the underlying lung is clear. This fluid partially obscures the left leaf of the diaphragm. Cardiac enlargement is apparent mainly in the region of the left ventricle. The aorta is very interesting (Fig. 1 and 2). The

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entire thoracic portion of the aorta is widened. Marked calcification is present in the arch and descending portion of the aorta. The soft-tissue density of the aortic wall extends from 1 to 1.5 cm. beyond the calcification. Since the visible calcification is in the intima or close to the intima, the apparent widening of the aortic shadow is due to thickening of the wall rather than dilatation of this vessel. The plain film of the abdomen shows a normal-sized liver and spleen. There was no dilatation of the small or large bowel. Extensive sclerosis of the vessels of the celiac axis, the descending aorta and pelvic vessels on both sides is seen. A small oval mottled calcification seen in the pelvis may be within a small uterine fibroid.

DR. KRANES: From the record I was led to believe that there was an area of consolidation in the left lower lobe, but that does not appear to have been so. There was merely a small amount of fluid. After seeing the films, I consider the likelihood of pulmonary infarction more remote than I had originally anticipated. I had wondered whether the circulatory disturbance several weeks before entry might have been due to venous rather than arterial disease, but the symptoms described are so clear-cut, indicating at least partial occlusion of one of the arteries of the leg, that the possibility of thrombophlebitis does not seem to be very strong. I think, therefore, that pulmonary infarction is not very likely. There are the same objections to mesenteric thrombosis that apply to any intra-abdominal disease; I have already stated them.

The pieces of this puzzle can be very neatly fitted together if one makes the assumption that this patient had a dissection of the aorta. If one assumes that the original intimal tear and dissection occurred three weeks before admission and that it occurred in the abdominal aorta, that might account for the circulatory insufficiency of the left leg. Then, after a quiescent period, the dissection proceeded upward and involved the intrathoracic portions of the aorta, causing the upper-abdominal and chest pain, perhaps dissecting along some of the intercostal arteries, producing the fluid seen in the left pleural cavity — a not uncommon finding with aortic dissections. The final episode would of course have been the ultimate external rupture occurring either in the pericardium or mediastinum, the usual terminal event.

Although a dissection of the aorta sounds very plausible, and I think it fits the picture extremely well, there are certain objections to it that it is only fair to list. In the first place, if I assume that the original dissection, to account for the leg symptoms, took place three weeks before entry, it seems strange that it was not preceded by any abdominal pain. The intimal tear and early dissection are usually quite painful — although cases have been recorded, and I think we have one here, in which the pain was relatively insignificant. She may have had some mild abdominal pain preceding the leg symptoms that was not sufficiently intense to report to her physician. Perhaps the leg symptoms were not due to the dissection but to some local thrombosis unrelated to the rest of the picture. With vessels as sclerotic as hers, it is only fair to assume that she may have had an independent local thrombosis at the site of an atheromatous plaque.

Another objection to aortic dissection is that in the great majority of cases the original tear usually involves not the abdominal aorta but the thoracic portion, commonly the ascending aorta or the arch. However, what bothers me chiefly about this explanation is the absence of hypertension. There was only one elevated blood pressure reading — 200 systolic, 80 diastolic — and that terminally. A normal blood pressure is a serious objection to the diagnosis of a dissecting aneurysm. If she were a younger person I should take the absence of hypertension somewhat more seriously. Elderly patients are occasionally seen in whom the intimal tear may take place at the site of an arteriosclerotic plaque rather than in an otherwise normal aorta. That occurs in the nonhypertensive group. If I am correct in the assumption that the patient had a dissecting aneurysm, the terminal episode would have been an external rupture of the adventitia into the pericardium or into the mediastinum. On the data presented here I do not quite see how I can differentiate the two. There was no evidence in favor of pericardial tamponade. What few data I have been given are more in keeping with a rupture into the mediastinum.

A PHYSICIAN: I should like to ask Dr. McCort if the psoas shadow was visible on the right.

DR. MCCORT: Yes; both psoas shadows are visible and symmetrical.

DR. JOHN T. QUINBY: What did you say about the thoracic descending aorta?

DR. MCCORT: It is widened, and this widening is apparently due to thickening of the wall. The inner margin of the wall is demarcated by the calcification; the outer, by the surrounding aerated lung. The increased distance between the margins indicates diffuse thickening of the aortic wall.

DR. ALLEN G. BRAILEY: Is anything known about what the blood pressure had usually been before the final illness?

DR. MCALLESTER: Usually around 140 systolic, 80 diastolic; occasionally as high as 170.

DR. WILLIAMS: I think that Dr. Kranes has given an excellent summary of what one should think of in a situation like this. We also were not satisfied with a diagnosis of myocardial infarction, not only for the reasons he mentioned but also because her temperature stayed at a rather consistent high level for days, which I thought was most unusual. Furthermore, there was the phenomenon of hypersensitivity to touch, which was quite impressive. We wondered if she was coming down with

herpes zoster — realizing that bilateral herpes is rather rare. On the last day I thought she had an expanding abdominal aneurysm. Finally the pain, which had been located constantly in the epigastrium, shifted up and became low substernal during the last few hours of life.

Clinical Diagnoses

Myocardial infarction, acute.
Arteriosclerotic heart disease.

Dr. Kranes' Diagnoses

Dissecting aneurysm of the aorta, with rupture into the pericardium or mediastinum.
Myocardial infarct, old.

Anatomical Diagnoses

Arteriosclerotic aneurysm of aortic arch, with rupture into left pleural cavity and with pseudodissection.
Myocardial infarct, old.

Pathological Discussion

Dr. Tracy B. Mallory: This patient was found to have an aneurysm that had ruptured into the left pleural cavity, but it was not considered to be a true dissecting aneurysm, although at first glance it strongly suggested the latter. It was a relatively small saccular aneurysm in the region of the arch. It had ruptured, and blood had dissected in the adventitial layer of the aorta as far down as the diaphragm, where it stopped very abruptly. In a true dissecting aneurysm the split is in the media, so muscle fibers are found both internal to and external to the newly formed blood channel. In this case the media was intact except at one point, where the rupture had occurred.

Saccular aneurysms of the thoracic aorta, of course, are classically caused by syphilis, but seventy-nine years of age would be an extraordinarily late age for a syphilitic aneurysm to present itself. Actually, in the material of this hospital, arteriosclerotic aneurysms are far commoner than syphilitic ones today. They are usually abdominal but can, as in this case, be thoracic. The heart was slightly hypertrophied and did show a scar of an old healed posterior infarct of the left ventricle, as was predicted.

Dr. Kranes: Was there any explanation for the circulatory difficulty of the legs, aside from the atherosclerosis?

Dr. Mallory: At the time of autopsy the leg arteries were all patent, though severely sclerotic. It is possible that there had been thrombosis at one time and that extensive recanalization had taken place.

CASE 37212

Presentation of Case

A twenty-seven-year-old man was admitted to the hospital because of abdominal distress.

Other than infectious mononucleosis nine months prior to entry, the patient had had no illnesses until five months before admission, when he became acutely ill. At that time he had marked weakness of the extremities, stiff neck, constipation and acute urinary retention. Because of cranial-nerve weakness, intravenous feedings were carried out for several days. A diagnosis of acute poliomyelitis was made. He remained in a hospital for the next two months, receiving physiotherapy and supportive care. Toward the end of this treatment there was good limb recovery but mild abdominal soreness commenced; this was attributed to muscular weakness. When he resumed normal diet and activity, mild epigastric pains and soreness awakened him during sleep. In the daytime, discomfort occurred approximately fifteen minutes after eating. One month prior to entry because of severe postprandial distress he was placed on an ulcer regimen consisting of hourly milk or Amphojel feedings, but this failed to give symptomatic remission. A gastrointestinal series made two weeks later reportedly demonstrated a preantral gastric ulcer with severe hypertrophic gastritis and giant rugae. Under medical management a diet was begun. One week prior to admission tarry stools were passed but were not checked for occult blood. The hemoglobin was 14.0 gm. Frequent emesis and increasing abdominal pain prompted hospital admission. A weight loss of fifteen pounds had been observed since the onset of the illness.

Physical examination revealed an agitated, well developed, tall, thin man in constant motion but in no immediate distress. The chest was clear to percussion and auscultation. There was no cardiac enlargement. Examination of the abdomen, which was flat and nontender with no palpable masses, was somewhat unsatisfactory, because of the patient's hyperactivity. Rectal examination was negative.

The temperature was 98.6°F., the pulse 80 and the respirations 30. The blood pressure was 135 systolic, 85 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 12.8 gm. and a white-cell count of 6200, with 77 per cent neutrophils. Two stools were guaiac positive, but several subsequent ones were guaiac negative. The vomitus was guaiac negative. The alkaline phosphatase was 7.6 units, the nonprotein nitrogen 18 mg., the albumin 4.54 gm., the globulin 2.06 gm., the serum amylase 26 units, the bilirubin 3.0 mg. direct and 4.2 mg. total and the urobilinogen 0.5 Ehrlich units per 100 cc.; the chloride was 100 milliequiv. and the sodium 130 milliequiv. per liter. The prothrom-

bin time was 57 seconds (normal, 17 seconds) and a cephalin-flocculation test was negative.

An abdominal film showed definite evidence of enlargement of both liver and spleen. In the gastrointestinal series a normal esophagus was visualized. Throughout the entire stomach, more marked, however, in the distal half, rugal folds were markedly irregularly enlarged (Fig. 1). A conspicuous defect about 3 cm. in diameter was noted in the inferior portion of the stomach several centimeters distal to the angle. The gastric antrum was considerably narrowed. There was a suggestion of ulceration along the lesser curvature, particularly in the region

FIGURE 1. *Barium-Meal Examination Showing Enlarged Irregular Rugae in Lower Half of Abdomen.*

of the antrum, although it may have represented barium caught in the folds of mucous membrane. Gastric emptying was delayed and the duodenal bulb was spastic but eventually filled without evidence of abnormality.

Gastroscopy was performed the following day, but due to lack of co-operation visualization was unsatisfactory. On the seventh hospital day the patient was agitated, demanded attention, complained loudly and twice during the night dressed to leave. Seventy-five mg. of Demerol provided only one-half to one-hour sedation. On the following day a gastroscopy was successfully carried out. Considerable amounts of coffee-ground matter were encountered, and cytologic examination of the fluid was interpreted as positive for tumor cells. The greater curvature appeared red, ragged, edematous and somewhat rigid in appearance. On the eleventh hospital day the liver edge was definitely palpable, as was the tip of the spleen. There was also a question of icterus of the scleras. Two days later a severe pruritic maculopapular erythematous eruption over the abdomen, elbows, arms and ankles occurred. Toward evening of the same day there was vomiting accompanied by epigastric crampy pain. The abdomen was tense and distended with diffuse tenderness throughout. Icterus could now be seen by artificial light and the serum bilirubin was reported as 4.0 mg. direct and 5.2 mg. total per 100 cc. A cephalin-flocculation test was now ++ in forty-eight hours. The white-cell count remained unchanged. An abdominal plain film showed gas-filled colon and scybalous masses without evidence of dilated small bowel or intraperitoneal air. On the nineteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MYLES P. BAKER*: The patient had a three months' history of increasing abdominal distress, epigastric pain and remarkably quick appearance of discomfort after meals. Fifteen minutes is a rather short time interval between eating and the development of pain attributable to an ulcer. The x-ray films made outside the hospital were said to reveal a gastric ulcer and remarkably enlarged gastric rugae.

DR. CHESTER M. JONES: That distress occurred sometimes even during meals.

DR. BAKER: I think the person whose stomach shows hypertrophic gastritis with these giant rugae is very likely to have transient or no relief from meals and is likely to continue on to vomiting and the picture suggesting partial pyloric block, as this man did.

The patient had tarry stools, the pain grew worse, and he manifested an emotional excitability and restlessness that may have been attributable in part to the antecedent central-nervous-system infection; he may have had an encephalitis along with the poliomyelitis. The laboratory data revealed an elevated serum bilirubin and a hypoprothrombinemia that was disproportionately abnormal in the light of the negative flocculation test and the absence of excess urobilinogen in the urine. I should take those findings, however, to mean definite liver damage. The urine specimen, it seems to me, must have had bile pigment, with a serum bilirubin of this level.

DR. DANIEL S. ELLIS: The serum bilirubin was not done until after the patient became clinically jaundiced. That is a mistake; it was not an admission test.

DR. BAKER: He was not jaundiced on admission. The x-ray films are pertinent to the discussion because they do show an enlarged liver and spleen,

*Physician, Massachusetts General Hospital.

these rugae, a filling defect, a narrow gastric antrum and a question of a lesser-curvature ulcer. Dr. Hanelin, I think I had better look at them.

DR. JOSEPH HANELIN: The stomach is about normal in size but is situated rather high in the abdomen, and the extremely prominent folds are well visualized in the films (Fig. 1). There was considerable delay before the antrum allowed any barium to squeeze through. This film shows better the defect that was described along the greater-curvature portion of the antrum. There is no evidence of a duodenal ulcer. The duodenal loop may be slightly widened and the folds within the loop are rather prominent. These films were made shortly after admission. The spleen and liver are both somewhat enlarged. At the time of examination two thoughts were expressed. The first was that this was gastritis; the second, that it was a question of some diffuse neoplasm such as, perhaps, a lymphoma.

DR. BAKER: Would you point out the ulcer on the lesser curvature?

DR. HANELIN: I am not certain of any definite ulcer in the stomach.

DR. BAKER: Is there a plain film of the abdomen? Is there some question of splenic enlargement?

DR. HANELIN: On a film taken later, — although the structures are magnified somewhat by this projection, — both liver and spleen appear to have increased in size.

DR. BAKER: It is not a very large spleen?

DR. HANELIN: No; not too large.

DR. BAKER: The gastroscopy on the eighth day showed, as you remember, a red, edematous, ragged, rigid greater curvature, and there was a positive cytologic examination for tumor cells. Of course this case is ideal for Dr. Benedict's contribution, namely, taking a biopsy and providing a diagnosis that ordinarily could only have been made by histologic examination of the resected specimen.

To go on with the history, there are a number of things that could cause the acute painful abdomen. I suppose he was considered a suspect for a perforation or some other abdominal emergency, but this seems to have quieted down, for he was not operated on for another few days. The association of an ulcerative gastric lesion with evident liver damage, such as I thought this man had prior to the examination of these films, would imply gastric carcinoma with liver metastases. Such a diagnosis would be supported by the cytologic smear. How often do we see false positive cytologic smears? I am told that the Cytological Laboratory is now going over its statistics and is not ready to present any definite figures as yet, but the impression I have is that positive smears in the stomachs that are found to have no malignant lesions are in the order of only 2 per cent.

DR. JONES: Two cytologic examinations were made from the secretions removed at each gastroscopy, and they both were positive.

DR. BAKER: The deterrent, as one reads the protocol, to the diagnosis of carcinoma of the stomach with liver metastases is the concomitant splenic enlargement, not only suggested by x-ray examination but apparently palpated by at least one observer. Could splenomegaly be a manifestation of portal hypertension with metastatic carcinoma of the liver? I see some of you shaking your heads, but it actually does happen. It is rare, but I have seen portal hypertension with cancer of the bile ducts involving the liver and producing subsequent splenomegaly. And there has been one instance of carcinoma of the sigmoid metastatic to the liver that has produced portal hypertension and splenomegaly. It must be borne in mind as a possible explanation of a palpable spleen when one strongly suspects cancer metastasizing to the liver. Splenomegaly raises the question of abdominal lymphoma, in view of the briefness of this man's history. Palpable splenomegaly is common in at least three fourths of the cases of abdominal lymphoma. It should be emphasized that there is no characteristic x-ray picture of lymphoma in the stomach, nor is there any picture as seen by the gastroscopist, as I understand it, that is unequivocally diagnostic of lymphoma. The picture that I have of what the gastroscopist sees in cases of lymphoma can be put into words, perhaps, but there is nothing that could not be simulated by an infiltrating carcinoma — the enlarged, very prominent, rather inelastic, stiffened rugae, or a circumscribed lesion with a small ulceration, which was not present here.

This man's history of a previous lymph-node enlargement, with the diagnosis of infectious mononucleosis that might not have been very well documented, the x-ray picture that is seen here with the giant rugae, and the apparent enlargement of the spleen all raise the question of lymphoma, and I suppose it was, as Dr. Hanelin said, considered by those in charge of the case. There is only one way to be sure of the diagnosis, and that is probably why the surgeons proceeded with what I suppose was an attempt at resection of the stomach.

My diagnosis would be cancer of the stomach with metastases to the liver producing jaundice and hypoprothrombinemia, rather than a gastric lymphoma — which would be a rare bird.

I remember reading somewhere that in people under thirty, although it is the age group in which lymphoma of the stomach is seen, there was only one lymphoma found for every 15 carcinomas of the stomach.

CLINICAL DIAGNOSIS

?Gastritis.
?Lymphoma of stomach.

DR. BAKER'S DIAGNOSIS

Carcinoma of the stomach, with metastases to the liver.

Anatomical Diagnoses

Carcinoma of the stomach with extensive generalized metastases (twenty-seven-year-old man).
(Jaundice.)

Pathological Discussion

Dr. Jones: The only comment that I would make would be that one had to obtain a biopsy to make a diagnosis. That is why the second gastroscopy was done, and the gastroscopic biopsy was positive in addition to the two cytologic smears that were made. On the basis of these three findings, two smears and a biopsy, a diagnosis was made of carcinoma of the stomach. The reason we operated on this patient was that he was having frankly obstructive symptoms that were not being relieved. It was the remote hope that we might relieve the obstruction so that the patient would have an easier course.

Figure 2. *Microscopical Section of Biopsy Showing Clump of Tumor Cells Within Mucosa.*

The x-ray films that were taken elsewhere were almost identical with these shown here. There was practically as much involvement as these films show this morning, but no definitive studies were carried out beyond the x-ray examination at that time.

Dr. Edward B. Benedict: I should agree with Dr. Baker that the gross appearance of the stomach at gastroscopy is not characteristic of either lymphoma, carcinoma or severe hypertrophic gastritis. These three can produce the same gross appearance, and I have been unable to decide on numerous occasions which was which without taking a biopsy. The biopsy in many cases has ruled out lymphoma, in a number of cases has ruled it in and in this case ruled in carcinoma.

Dr. Tracy B. Mallory: I have some photomicrographs of the sections that were made from the gastroscopic biopsy specimen. It is quite evident that this biopsy was not taken from the center of the lesion but at some distance to one side. There is a single cluster of cells that are entirely different in character from the normal cells of the neighboring glands (Fig. 2). These cells have giant-sized nuclei that are very hyperchromatic and are cytologically characteristic of malignant cells. They seem to be lying in an endothelial-walled tube, presumably a lymphatic in the mucosa. On this basis, since invasion of lymphatics was demonstrable we thought we were justified in making an unequivocal diagnosis of carcinoma. A short time later an exploratory operation was performed, and diffuse involvement with neoplasm of the major portion of the stomach was discovered; there were multiple small metastases in the liver as well. It was decided that the lesion was incurable, so resection was not attempted. The patient died in a few weeks and came to autopsy. At that time it was found that the tumor had apparently grown along the splenic vessels into the spleen. This had produced thrombosis of the splenic vein and some splenomegaly (330 gm.). Metastasis of carcinoma to the spleen is of course very unusual, but infiltration of the spleen from the hilus is not at all uncommon; in fact, it is a very frequent occurrence with cancer of the tail of the pancreas and is by no means rare in carcinoma of the stomach. The submucosa of the stomach was extensively infiltrated with tumor bulging the mucosa and producing the enlarged rugae. Only one area about 6 cm. in diameter along the greater curvature was shallowly ulcerated.

Dr. Jones: Could I ask one question? It seemed to me at the time that if there was lymphoma of the stomach a biopsy would almost certainly show it, since it tends to be a very diffuse process. A lymphoma producing as much change in the stomach would hardly have been missed.

Dr. Mallory: That is perfectly reasonable. Dr. Benedict has found a high percentage of positive biopsies in cases of lymphoma.

Dr. Baker: The Cytological Laboratory tells me that 6 negative smears were found on 6 proved cases of lymphoma of the stomach.

Dr. Jones: Therefore biopsy is better than cytologic specimens.

A Physician: Were there any brain metastases?

Dr. E. Peirson Richardson, Jr.: I believe not — at least none that were recognizable grossly.

Dr. Mallory: Metastases were present, however, in almost all the other viscera. The involved lymph nodes at the porta hepatis compressed the bile ducts sufficiently to cause the jaundice.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal

Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

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MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

THE SHATTUCK LECTURESHIP

ON THE occasion of the publication of the fifty-second annual Shattuck Lecture of the Massachusetts Medical Society, an account of the history of this traditional exercise may be of interest, particularly in view of the fact that the lecture has once again been delivered by a distinguished foreign visitor.

George Cheyne Shattuck, the elder, was born in Templeton, Massachusetts, in what is now the Worcester North District of the Society, in 1784, the youngest son of Dr. Benjamin and Lucy Barron Shattuck. His environment and the fact that he was named for George Cheyne, a London and Bath physician who practiced between 1671 and 1743, made it almost inevitable that he should enter his father's profession. He consequently matriculated at the University of Pennsylvania Medical School after graduating from Dartmouth College, and received his doctor's degree in 1807.

A practitioner of medicine in Boston from 1807 until his death in 1854, he delivered the annual discourse of the Massachusetts Medical Society in 1828 and was the Society's president from 1836 to 1840. A generous benefactor of both Dartmouth and Harvard colleges, he established the Shattuck professorship of pathological anatomy at Harvard Medical School in 1853.

Dr. Shattuck, on his death, bequeathed jointly to the Massachusetts Medical Society, the Massachusetts Society for Promoting Agriculture and the Massachusetts Charitable Mechanic Association the sum of $10,000, to accumulate for three years, after which a third part should be paid to the Medical Society

> . . . in special confidence that the said society shall carefully invest the amount which it may thus receive, and apply the net interest and income thereof from time to time, in the discretion of said society or its government, to the collection and publication, annually by some suitable person or persons, of historical or other essays on the climate of said commonwealth, on the diseases of its inhabitants, and on such other subjects as the said society or its government may select.

In 1877 the Council directed the Committee on Publications to offer prizes out of the fund, and this was done, four essays being handed in, "three of them of such merit that it was difficult to select the best." Subsequently no essay deemed worthy of consideration was submitted, and in 1888 the following resolution was introduced at the annual meeting of the Council, Dr. George C. Shattuck, the younger, being chairman of the Committee on Publications:

> *Resolved*: That the Committee on Publications be instructed to provide for a lecture, to be called the Shattuck Lecture, on some subject in accordance with what is specified in the will of the late Dr. Shattuck, the lecture to be delivered at the annual meeting of the Society, the honorarium for it and the publication of it to be defrayed from the income of the Shattuck Fund.
>
> *Resolved*: That the income of the Shattuck Fund not required for the expenses of the lectureship shall be used for the printing of the Medical Communications of the Society.

The recommendations were adopted, and in 1890 the first lecture of the series was delivered by Dr. George B. Shattuck, grandson of the donor, on the subject "Influenza in Massachusetts."

A long series of distinguished physicians have since then succeeded to the lectureship, one of the most eminent — although, paradoxically, not a physician — being the current lecturer, Sir Charles Harington, director of the National Institute for Medical Research of England.

CIVIL DEFENSE

The interest of the public in matters pertaining to civil defense may wax and wane with the news reports from the Korean front, but those who are directly or indirectly engaged in establishing this prodigious organization cannot rest until its completion. Much progress is being made, and since all physicians and surgeons must perforce be involved in one or another ramification of the project it is essential that they keep themselves informed of the major developments. These are being detailed in civil-defense bulletins issued by the Committee on Emergency Medical Service of the Massachusetts Medical Society, by the Massachusetts Hospital Association and by the Hospital and Medical Section of the Massachusetts Civil Defense Agency.

At the State level the Civil Defense Organization is made up of seven divisions consisting of Medical and Health; Rescue, Transportation and Evacuation; Police; Fire; Communication; Utilities; and Civilian War Aid. The Medical and Health Division, which is headed by Dr. Vlado A. Getting, is subdivided into twelve sections, which cover all details of medical care. Each of the sections of the Medical and Health Division is sponsored by several voluntary and governmental agencies, among which the Massachusetts Medical Society is playing a major role.

In addition to the State organization, Massachusetts is divided into nine Civil Defense Regions, with similar organizations at that level. It is essential that district medical societies establish an intimate rapport with each of these nine Civil Defense Regions. In some instances, as in Berkshire, a single county medical society is concerned, whereas in the larger regions such as Region V, the Boston area, five district medical societies are involved. Obviously, it will take time to work out operational details, but this end will be more readily attained if all physicians keep themselves informed of the progress that is being made.

Civil Defense Bulletin No. 2, issued by the associate chief of the Hospital and Medical Section of the Massachusetts Civil Defense Agency, is of particular interest, since it lists the primary target areas, defines the disaster and reserve areas and describes the function of hospitals in these areas. Detailed estimates of the rate and intended flow of casualties are given, and the specific steps that each hospital should immediately take are outlined. The need for every hospital to have a disaster plan is emphasized, but it is also pointed out that extravagant expenditures and stockpiling of equipment are not wise at this time.

Perfection in so elaborate a program cannot be expected until its functioning has been put to the test of actual operation. Many will disagree with some of the specific recommendations. Thus a 50-bed ward team consisting of 3 doctors, 4 interns, 8 nurses and 2 orderlies, as listed in the staffing tables recommended in this bulletin, might seem to be far in excess of actual requirements. A team of this size should be able to handle two or three times that number of patients if proper triage is carried out at the time of admission to the hospital. Likewise, operating teams consisting of 2 surgeons, a nurse and an anesthetist will prove superabundant in many cases and inadequate in others. These are facts that are fully appreciated by the Civil Defense Agency, and it is made clear in the bulletin that the staffing tables are purely tentative and should be regarded as a suggestion rather than a directive. This is in accordance with the experience of surgeons in the last war, who recognized the need of extreme flexibility in the establishment of ward teams, shock teams and operating-room teams.

In Civil Defense Bulletin No. 1 issued by the Massachusetts Hospital Association, and also in Civil Defense Bulletin No. 1 issued by the Committee on Emergency Medical Service of the Massachu-

setts Medical Society, certain specific emergency instructions to physicians, nurses, dentists and other health workers are detailed. Some of these recommendations are open to question and certainly require further clarification. For example, this instruction is given: "In burn cases use ointment with a minimum amount of dressing." It is not clear whether this statement applies as an emergency measure or whether it is an attempt at treatment at the level of the casualty hospital. Incorrectly interpreted, it can lead to considerable retrogression in the management of burns. It would seem better to describe in detail the emergency management of burns at the level of first-aid teams and to permit surgeons at the level of the casualty hospitals to use their own judgment, which of course must be tempered by the extraordinary number of casualties that may be expected.

Similarly, in the same bulletins the following statement appears: "With limited supplies of blood and blood substitutes, patients suffering from burns should be treated for shock with at least one quart a day of a solution containing one-half teaspoonful of baking soda and one teaspoonful of salt in water."

Although it is obvious that such a solution should be taken by mouth, it is not clearly stated, and the association of blood, blood substitutes and shock with a quart of any type of solution might lead to disastrous results if the instructions were read under the pressure of an acute emergency. Furthermore, the ingestion of a solution of salt for the treatment of shock due to oligemia is a highly controversial issue, and it would seem wise to have operational details such as these prepared by a carefully selected committee of experts and so worded that confusion cannot arise.

These are merely examples of the difficulties that any central agency encounters when it attempts to give specific direction to workers at the operational level. It is vital, therefore, that the planning be pushed to completion now, while there is still ample time to study, review and revise the infinity of details that this task comprises. It is likewise vital that all physicians and surgeons keep abreast of the development, step by step.

SLEEP HABITS IN INFANCY

Many of the references to sleep found in the literature are cultural rather than scientific in their content; they are based on its general desirability rather than on any studies of its physiologic nature. One of the most familiar of these allusions states almost axiomatically that sleep it is a blessed thing, beloved from pole to pole, and almost never have any attempts been made to shake the sublime faith that mankind has in this statement.

Wordsworth, somewhat obscurely, likens birth to "a sleep and a forgetting," but in general the writers are unequivocally in its favor and decry its interruption; the accepted synonymity of sleep and cohabitation presents a paradox that has not been adequately explained.

The psychoanalysts long since discovered the dream state, an occasional accompaniment of sleep, as a limitless field for imaginative exploitation, second only to sex itself. Such a wealth of material has been unearthed from the mind released in sleep that the importance of daydreaming has been largely overshadowed.

Factual studies of sleep, however, have also been made. As long ago as 1927 and 1928 the Institute of Child Welfare of the University of Minnesota, applying the scientific technic, discovered not only that country children slept shorter hours than city children but also that neither group came up to the standards somewhat arbitrarily established by their parents and pediatricians, if any.

The most recent investigations, released by the Office of Press Relations of the University of Chicago, were reported early in May to the Federation of American Societies for Experimental Biology. These studies, conducted on a lower age group, bear out the conclusions of the earlier report from the University of Minnesota — babies, too, sleep less than was formerly believed or than their mothers think they should.

Contrary to a fixed parental idea, nevertheless, even three-week-old infants take the majority of their fifteen hours of sleep at night. As their weeks advance, the young mother will be delighted to

learn, the night sleep lengthens as the day sleep shortens.

The studies, financed by Swift and Company, indicate no difference in sleep habits between carnivorous infants and those maintained on a vegetarian diet.

ACCENT ON PREVENTION

It is said that $8,000,000,000, or nearly $4 out of each $100 spent in the United States during 1949, went for medical care. But no one knows how much of the money went for Hadacol or Dolcine tablets, how much to pay the physician, hospital or chiropractor or how much for health and accident insurance.

A survey by Columbia University under the direction of Professor Oscar Serbein, Jr., of the Graduate School of Business, is expected to ascertain and publicize such items as the number of individuals covered by medical and hospital prepayment plans, the types of illness covered, the medical services provided for combating them and the possibilities for further progress in such plans.

No doubt the job will be well done. Facts are needed first of all. It is important to understand the cost of medical care.

It is even more important to understand and to worry about the necessity for so much medical care. Who knows how much of the $8,000,000,000 might have been saved if our housing and food and our emotional and mental equilibrium were what they ought to be? Of course medical care costs more than it should. It will cost as much no matter how the money is provided.

The millennium will be approaching, not when all medical care is paid for in advance or when its cost is more equitably distributed, but when the world has learned how not to need so much of it.

Meeting of the Superintendents of Insane Hospitals. — A paper was read by Dr. J. M. Galt, of Va., on the Impropriety of treating persons afflicted with other diseases in the same institution with the insane. Dr. N. Cutter, of Mass., read a paper on the nature of stramonium and its value in the treatment of the insane.

Boston M. & S. J., *May 28, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Anthony — Francis W. Anthony, M.D., of Haverhill, died on March 27. He was in his ninety-third year.

Dr. Anthony received his degree from Harvard Medical School in 1888. He was medical examiner of Essex County for twenty-five years and was secretary of the Pentucket Association of Physicians.

A son, three grandchildren and a sister survive.

Martin — Edward Martin, M.D., of Milton, died on April 8. He was in his sixty-seventh year.

Dr. Martin received his degree from Tufts College Medical School in 1911. He had been a staff member of Homberg Infirmary, Massachusetts Institute of Technology, and Massachusetts Women's Hospital, a director of the Irene Hyde Memorial Clinic and medical director of the Huntington Avenue Branch, Y. M. C. A. He was a fellow of the American Medical Association.

His widow, a son, a daughter, a brother and a sister survive.

Pratt — Charles A. Pratt, M.D., of New Bedford, died on April 3. He was in his eighty-ninth year.

Dr. Pratt received his degree from Harvard Medical School in 1891. He was a fellow of the American Medical Association.

His widow, three sons, two daughters and eleven grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The June schedule for Consultation Clinics for Crippled Children in Massachusetts under the provision of the Social Security Act follows:

Orthopedic Clinics	Date	Clinic Consultant
Lowell	June 1	Albert H. Brewster
Salem	June 4	Paul W. Hugenberger
Haverhill	June 6	William T. Green
Greenfield	June 7	Charles L. Sturdevant
Lynn*	June 11	Daniel M. Killoran John J. Crowley
Gardner	June 12	Carter R. Rowe
Brockton	June 14	George W. Van Gorder
Worcester	June 15	John W. O'Meara
Fall River	June 25	David S. Grice
Springfield	June 26	Garry deN. Hough, Jr.
Hyannis	June 28	Paul L. Norton

Rheumatic Fever Clinics	Dates
North Reading	June 5, 12, 19, 26
Fitchburg	June 6, 13, 20, 27

Plastic Clinics	Consultant
Eastern Massachusetts	Bradford Cannon Semi-monthly
Western Massachusetts	Joseph M. Baker Monthly

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

CORRESPONDENCE

A DISAGREEMENT

To the Editor: I was extremely interested in Drs. Braun and Comeau's article, "The Importance of a High-Pitched Squeaking Systolic Murmur in the Diagnosis of Aortic Stenosis and Calcification of the Aortic Valve," which appeared in the April 5th issue of the *New England Journal of Medicine*. There are, however, a number of inconsistencies in this report that are not reconcilable with existent knowledge of cardiac pathology and physiology.

There are three prime factors to which I take exception: (1) the presence of an increased or normal second sound; (2) the assumption that calcification of the aortic valve leaflets and the aortic ring per se is definitive evidence of aortic stenosis;
(3) that a wide pulse pressure is not an infrequent finding in aortic stenosis.

Primary aortic arteriosclerosis at the points of greatest wear is common. On occasion the annulus fibrosus is involved. This process starts at the base of the valves and proceeds toward the free margin and reaches the valvular surface. An accompanying fibrosis disturbs the valve and on occasion produces an insufficiency. The pathologic change is in a direction opposite to that of rheumatic fever, which begins neither at the free edge nor at the base but at the margin of closure. In many instances aortic calcific changes are superimposed on a previous rheumatic valvulitis, the latter proved by microscopic changes indicative of rheumatic fever in the adjacent myocardium.

Aortic calcification in the supravalvular portion is frequently seen in luetic aortitis, and it is well known that the supravalvular aorta, immediately above the sinus of Valsalva, is usually spared in atherosclerosis and arteriosclerosis of the aged, with the aortic lesions increasing in severity as one proceeds distally down the aorta; however, a lesion just proximal to the arch may produce enough turbulence during systolic ejection to bring about a harsh Grade II-III murmur.

A wide pulse pressure is not unusual in peripheral arteriosclerosis. In a dynamic aortic stenosis there is a decreased stroke output due to the obstruction (pulsus parvus et tardus), with a narrowed pulse pressure.

In view of the pathology of aortic stenosis, it is not understood how the foreshortened valves are able to close with enough movement to produce an adequate or increased second tone. The presence of a normal or increased aortic second sound (the latter may be due to concomitant hypertension) is used, in the presence of an aortic systolic murmur, to differentiate the presence of atherosclerotic changes of the aorta and aortic valvular disease. Dancing calcification in fluoroscopy would imply adequate valve movement incompatible with a *dynamic* stenosis. A beginning stenotic lesion may afford only a murmur, but so may supravalvular sclerosis. In the case histories cited by the authors to substantiate their premises, calcification of the aortic-valve leaflets and aortic ring is mentioned, but actual measurements of the aortic-valve ring and the status of the aortic commissures and the supravalvular aorta are not recorded (except in Case 1).

In aged persons, prone to atherosclerosis and arteriosclerosis of the aorta, with or without demonstrable aortic-valve calcification, in the absence of other known and established confirmatory signs it is hazardous to postulate aortic valvular stenosis, which carries an entirely different prognostic picture from simple generalized arterio-sclerosis, on the basis of a peculiar systolic murmur alone.

JOHN L. SWITZER, M.S., M.D.

Chicago, Illinois

Dr. Switzer's letter was submitted to Dr. Comeau, who makes the following reply:

Thank you for forwarding Dr. Switzer's letter to me. In Dr. Braun's absence from this country I should like to make the following comments:

In answer to Exception 1, it does not seem unreasonable or inconsistent with our knowledge of aortic stenosis and valvular dynamics to expect and to find the aortic second sound and pulse pressure normal in the lesser degrees of aortic stenosis. The title of the paper and our comment in Case 2 point out that we do not necessarily make the assumption that Dr. Switzer claims in his second exception. In regard to Exception 3, if arterial hypertension exists, as it often does, it may overshadow a slight degree of aortic stenosis and result in an accentuated second aortic sound and a wide pulse pressure. We were, perhaps, remiss in not amplifying this point more fully in our report.

I would be interested to know on what sound evidence Dr. Switzer bases the statement that arteriosclerotic changes just proximal to the aortic arch produce a harsh murmur. Although it may be so, certainly many persons are seen at postmortem with the type of arteriosclerosis described in whom no murmur was heard during life.

I cannot agree with Dr. Switzer that movement of a calcified aortic valve implies *adequate* valvular function. It has been firmly established that motion of the calcific mass is seen fluoroscopically in calcareous aortic stenosis. Moreover, the validity of attempting to estimate valvular function in the manner that Dr. Switzer has mentioned is open to question. The competent pathologist will often refuse to draw authoritative conclusions in regard to the functional capacity of the heart or its components even though obvious damage exists.

We remain convinced that if one awaits the so-called established confirmatory signs of aortic stenosis before making that diagnosis many cases will be overlooked.

WILFRID J. COMEAU, M.D.

Bangor, Maine

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Human Sterilization: Techniques of permanent conception control. By Robert L. Dickinson, M.D., and Clarence J. Gamble, M.D. 4°, paper, 40 pp., with 31 illustrations. Winston-Salem, North Carolina: Human Betterment League of North Carolina, 1950. 25c.

This pamphlet summarizes the surgical methods used in human sterilization.

Communicable Diseases. Edited by Roscoe L. Pullen, M.D., professor of graduate medicine, director of the division of graduate medicine, and vice-dean of the School of Medicine, Tulane University of Louisiana, senior visiting physician, Charity Hospital of Louisiana at New Orleans, consultant in medicine, Veterans Administration Hospital, New Orleans, consultant in medicine, Veterans Administration Hospital, New Orleans, and consultant to the Surgeon General, Department of the Army, Washington, D. C. 4°, cloth, 1035 pp., with 253 illustrations. Philadelphia: Lea and Febiger, 1950. $20.00.

This comprehensive treatise is the joint work of 53 specialists in their particular fields. The subject has been covered very broadly, including the rickettsial and parasitic diseases and botulism. The book is well published and should be in all medical libraries and in the libraries of practicing physicians.

Having a Baby: A guide for expectant parents. By Alan F. Guttmacher, M.D., associate professor of obstetrics, Johns Hopkins University School of Medicine, visiting obstetrician, Johns Hopkins Hospital, and chief of obstetrics, Sinai Hospital, Baltimore, Maryland. Second printing. 12°, paper, 191 pp., with 8 illustrations by Leon Schlossberg. New York: New American Library of World Literature, Incorporated, 1950. 25c.

This small book is a drastic revision of *Into This Universe: The Story of The Human Birth* (1937) and *The Story of Human Birth* (1947) by the same author. In this condensed version much material had to be omitted to bring the volume down

to pocket size, and the text has been revised and brought up to date. The first chapter, entitled "The Accident of Birth," is entirely new, being substituted for the chapter in the previous edition called "A Sixteenth Century Birth." This small inexpensive manual by an outstanding obstetrician should prove valuable to expectant mothers.

Recent Advances in Chemotherapy. By G. M. Findlay, C.B.E., Sc.D., M.D., F.R.C.P., editor, *Abstracts of World Medicine* and *Abstracts of World Surgery, Gynaecology and Obstetrics*, British Medical Association, London. Third edition. Vol. I. 12°, cloth, 625 pp., with illustrations and tables. Philadelphia: Blakiston Company, 1950. $7.50.

The first and second editions of this progress manual were published in 1930 and 1939 in single volumes. The advances in the subject have been so great in the intervening time that it will take three volumes for this third edition. The present volume is devoted to a short history of chemotherapy and to its use in diseases due to insects, helminthic diseases, amebiasis, babesiasis and other protozoal infections, leishmaniasis and trypanosomiasis. The various chapters are documented with lists of references to the recent literature. There are author and subject indexes. The text was printed in Great Britain. The set should be in all collections on the subject.

Williams Obstetrics. By Nicholson J. Eastman, M.D., professor of obstetrics, Johns Hopkins University School of Medicine, and obstetrician-in-chief, Johns Hopkins Hospital. Tenth edition. 8°, cloth, 1176 pp., with 659 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1950. $12.50.

This textbook was first published by Dr. J. W. Williams in 1902. It has enjoyed a well deserved popularity. The present tenth edition has been thoroughly revised by Dr. Eastman and brought up to date. Much material has been added, and many new illustrations have been included. The publishing is excellent, and the book is recommended for all medical libraries and to all obstetricians.

Klinische Pathologie der Blutkrankheiten. By Professor Dr. Rudolf Schoen, director Medizinischen Universitätsklinik zu Göttingen: and Professor Dr. Walter Tischendorf, physician-in-chief, Medizinischen Universitätsklinik zu Göttingen. 8°, cloth, 521 pp., with 100 illustrations. Stuttgart: Georg Thieme, 1950. DM 57.

This new work on the clinical pathology of blood diseases is well organized and well written in typical German style. The bibliographies appended to the various chapters are extensive in scope. There are good indexes of subjects and authors. The publishing is excellent. The book should be in all collections on the subject.

Management of Peripheral Arterial Diseases. By Saul S. Samuels, A.M., M.D., chief, Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York City, consulting vascular surgeon, Long Beach Hospital, Long Beach, New York, director and attending angiologist, Brooklyn Hebrew Home and Hospital for Aged, Brooklyn, New York, editor-in-chief, *Angiology*, and president, Angiology Research Foundation. 8°, cloth, 345 pp., with 112 illustrations. New York: Oxford University Press, 1950. $7.50.

This monograph, which was first published in 1936, is now revised and enlarged from *The Diagnosis and Treatment of Diseases of the Peripheral Arteries*, issued in 1940. The author has had an extensive experience with thousands of cases of gangrene over a period of twenty-five years and believes that the responsibility for such cases should be given solely to one properly trained member of the hospital staff. This book gives the results of his vast experience in as great detail as possible. Naturally, the largest portion of the text is used for a discussion of thromboangiitis obliterans and arteriosclerosis obliterans. The remainder is devoted to the other diseases of the peripheral arteries. The text is concluded with an interesting chapter on the medicolegal aspects of the subject. The material is well arranged and well written. There are author and subject indexes. The book is well published and should be in all medical libraries and in the libraries of physicians and surgeons.

Non-Gonococcal Urethritis: Including the genital manifestations of local and systemic diseases and infestations of the urinary tract with protozoa, metazoa and fungi. By A. H. Harkness, M.R.C.S., L.R.C.P., joint director of the Endell Street Clinic, St. Peter's and St. Paul's hospitals (Institute of Urology), lecturer to the Institute of Urology, consultant in venereal diseases to St. Charles' Hospital, civil consultant in venereal diseases to the Royal Navy, physician to the London Skin Hospital and vice-president of the British Society for the Study of Venereal Diseases. 8°, cloth, 424 pp., with 167 illustrations. Baltimore: Williams and Wilkins Company, 1950. $10.00.

The author has been prompted to write this extensive monograph by the facts that nongonococcal urethritis was present in at least 70 per cent of his patients affected with venereal disease and that the antibiotics were ineffective in most of his cases of nongonococcal disease. The disease is discussed thoroughly, and the material is well arranged. The publishing is excellent. The printing was done in Great Britain. There are indexes of authors and subjects. The book should be in all medical libraries and available to all practicing physicians.

Maternity Care in Two Counties: Gibson County, Tennessee, and Pike County, Mississippi, 1940-41, 1943-44. By Frank E. Whitacre, M.D., chief, Division of Gynecology and Obstetrics, University of Tennessee College of Medicine; and Ellen W. Jones, M.P.H., statistician, Commonwealth Fund. 8°, paper, 165 pp., with 56 tables. New York: Commonwealth Fund, 1950. 50c.

This monograph constitutes a thorough study of all the phases of maternity care in two selected counties. Among the factors discussed are ante-partum care; toxemia, syphilis and tuberculosis in pregnancy; management of labor and delivery; post-partum care; maternal mortality; and mortality of babies. The publishing is excellent and there is a good index.

The Merck Manual of Diagnosis and Therapy: A source of ready reference for the physician. Eighth edition. 16°, cloth, 1592 pp. Rahway, New Jersey: Merck and Company, Incorporated, 1950. $5.00.

This new edition of a standard reference manual, first published in 1899 and last in 1940, has been thoroughly revised and brought up to date. New material up to May 12, 1950, has been included. The material is divided into two parts. The first part, on diagnosis and therapy, comprising the major portion of the book, is arranged alphabetically, according to subjects and systems of the body, and includes 1175 prescriptions. The second is devoted to procedures, diet and tables.

New or expanded chapters comprise those on nutritional deficiencies, radiation reactions and injuries, including those due to atomic energy, allergies and antihistamines, psychoneuroses, drug addiction, dental emergencies, prenatal and postnatal care and the care of premature infants. The medical experience gained during World War II is reflected throughout the text. The latest information available up to the time of printing on the antibiotics, crystalline vitamin B_{12} and cortisone and ACTH is found in the appropriate chapters. A comprehensive index of 22 pages forms the third part of the book. The text is well printed, and the volume is light in weight and easy to handle. It is inexpensive and should be in all medical libraries and should prove valuable to all practicing physicians.

Lectures on Medicine to Nurses. By A. E. Clark-Kennedy, M.D., F.R.C.P., fellow of Corpus Christi College, Cambridge, physician to the London Hospital and dean of the Medical School. With a foreword by Miss Clare Alexander, matron of the London Hospital. 8°, cloth, 288 pp., with 28 illustrations. Baltimore: Williams and Wilkins Company, 1950. $3.50.

In this manual for nurses the author has endeavored to furnish the essentials of medicine required by them in their daily work. The common diseases, conditions and symptoms and treatment are discussed in a practical manner. The text is well written and well arranged. There is an index, and the small book is well published. The printing was done in Great Britain. The manual should prove useful to nurses.

Peptic Ulcer. By A. C. Ivy, Ph.D., M.D., D.Sc., LL.D., vice-president of the University of Illinois, in charge of Chicago Professional Colleges, professor of physiology and chairman of the Department of Clinical Science, University of Illinois College of Medicine; M. I. Grossman, Ph.D., M.D., associate professor of physiology in the Department of Clinical Science, University of Illinois College of Medicine; and William H. Bachrach, Ph.D., M.D., research associate in physiology, University of Southern California School of Medicine. 8°, cloth, 1144 pp., with 137 illustrations and 210 tables. Philadelphia: Blakiston Company, 1950. $14.00.

This treatise on one of the most common and costly diseases is comprehensive in its scope and cyclopedic in its coverage of the subject. The pertinent literature on all aspects of peptic ulcer is reviewed and noted. The text is divided into four main sections: introduction to the problem of peptic ulcer; pathogenesis; diagnosis; and treatment. The chapter on psychosomatic etiology is especially interesting and illuminating. The text is well written and the material well arranged. Extensive bibliographies are appended to the various chapters or sections. The book is well published and is recommended for all medical libraries and should be available to all practicing physicians, internists and gastroenterologists.

Buchanan's Manual of Anatomy. Edited by F. Wood Jones, D.Sc. (Lond., Adelaide and Melb.), M.Sc. (Manch.), M.B., B.S. (Lond.), F.R.S., F.R.C.S., Eng., Sir William Collins Professor of Human and Comparative Anatomy at the Royal College of Surgeons of England. Eighth edition. 8°, cloth, 1616 pp., with 847 illustrations. Baltimore: Williams and Wilkins Company, 1950. $8.50.

This standard British treatise on human anatomy, first published in 1906, has been thoroughly revised for its eighth edition without change in the format of the work. The printing was done in Great Britain.

Modern Practice in Dermatology. Edited by G. B. Mitchell-Heggs, O.B.E., M.D., F.R.C.P., physician-in-charge, Skin Department, St. Mary's Hospital and Medical School, London, physician, St. John's Hospital for Diseases of the Skin and Institute of Dermatology, University of London, and member, Advisory Panel on Dermatitis, Ministry of Labour and National Service. 8°, cloth, 836 pp., with 319 illustrations. New York: Paul B. Hoeber, Incorporated, 1950. $12.50.

This British treatise on dermatology is the joint work of 41 contributors. The material covers the whole field of the subject, including a chapter on remedies and one on the social aspects of diseases of the skin. The material is well organized, and the publishing is excellent. The illustrations are good. The printing was done in Great Britain. The book should be in all medical libraries and in all collections on dermatology.

The Pathology of Internal Diseases. By William Boyd, M.D., Dipl. Psych., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (Canada), LL.D. (Sask.), D.Sc. (Man.), M.D. (Oslo), F.R.S. (Canada), professor of pathology and bacteriology, University of Toronto. Fifth edition. 8°, cloth, 866 pp., with 391 illustrations. Philadelphia: Lea and Febiger, 1950. $11.00.

Dr. Boyd has revised this new edition of his standard textbook. New sections have been included and others rewritten. There is a new chapter on diseases of the bones and joints and new sections on renal anoxia, the diffuse collagen diseases, congenital hemolytic disease, myeloid metaplasia, primary splenic neutropenia, the anemia of infection, folic acid deficiency anemia, histiocytic medullary reticulosis, temporal arteritis, Loeffler's pneumonia, anthracosilicosis, beryllium and bauxite pneumonitis, pulmonary moniliasis, the relation of the kidney to hypertension, the renal lesions in diabetes, Kernohan's new classification of the gliomas, Ellis' classification of glomerulonephritis, idiopathic pulmonary hemosiderosis, cortisone in rheumatoid arthritis and choline-deficiency hypertension. The publishing is excellent, and the book should be in all medical libraries and should prove useful to all physicians.

Manual of Rheumatic Diseases. By W. Paul Holbrook, M.D., and Donald F. Hill, M.D., Tucson, Arizona. With the assistance of Charles A. L. Stephens, Jr., M.D. 8°, cloth, 182 pp., with 119 illustrations. Chicago: Year Book Publishers, Incorporated, 1950. $4.25.

This manual has been written for the general practitioner. The material has been condensed and simplified. Emphasis has been placed on office and home procedures of treatment.

Pye's Surgical Handicraft: A manual of surgical manipulations, minor surgery, and other matters connected with the work of surgical dressers, house surgeons and practitioners. Edited by Hamilton Bailey, F.R.C.S. Eng., surgeon and surgeon-in-charge of the Genitourinary Department, Royal Northern Hospital, London, senior surgeon, St. Vincent's Clinic and the Italian Hospital, surgeon, Consolation Hospital, Lambeth, general surgeon, Metropolitan Ear, Nose and Throat Hospital, London, and consulting surgeon, County Hospital, Chatham, Potter's Bar Hospital, and Clacton Hospital. Sixteenth edition. 8°, cloth, 724 pp., with 830 illustrations. Baltimore: Williams and Wilkins Company, 1950. $6.00.

The first edition of this popular British handbook was published in 1884. The book is the joint effort of 50 contributors — 2 from the United States for the first time. It is essentially a work on surgical treatment. This edition has been revised and brought up to date. The material is well arranged, and the publishing is good. The printing was done in Great Britain.

A Guide to Psychiatric Books with a Suggested Basic Reading List. By Karl A. Menninger, M.D., general director of the Department of Education, Menninger Foundation, Topeka, Kansas. With the collaboration of George Devereux, Ph.D., lecturer in anthropology, Menninger School of Psychiatry and Topeka Institute for Psychoanalysis, Topeka, Kansas. 8°, cloth, 148 pp. New York: Grune and Stratton, 1950. $3.50. (Menninger Clinic Monograph Series No. 7.)

The authors have divided their text into two main divisions, bibliography and a basic reading list. The bibliography of 1193 books is subdivided into four parts: the basic disciplines, including the philosophy of science, logic and methodology, neurology, psychology and the social sciences, numbering 420 titles; psychiatry; psychiatric therapies; and preventive psychiatry and mental hygiene. Because of the obvious difficulty of using such a long list discriminately the authors have starred certain books of outstanding significance. The second division, a suggested basic psychiatric reading list of 89 titles, is a revision of the list published by Dr. Menninger in 1938 in the bulletin of his Clinic. There is an author index, and the small volume is well published. It is recommended for all medical libraries and all collections on psychiatry.

Light Therapy. By Richard Kovacs, M.D., professor of physical medicine, New York Polyclinic Medical School and Hospital. 8°, cloth, 112 pp., with 28 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.25. (Publication Number 57, American Lecture Series.)

This small monograph summarizes the present knowledge of light therapy. The material is divided into four parts: history, infrared and luminous radiation and ultraviolet radiation. A bibliography and an index are appended to the text.

Asphyxia Neonatorum: Its relation to the fetal blood, circulation and respiration and its effects upon the brain. By William F. Windle, Ph.D., Sc.D., professor of anatomy and chairman of the Department of Anatomy, University of Pennsylvania School of Medicine. 8°, cloth, 70 pp., with 9 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $2.00. (Publication Number 52, American Lecture Series.)

The text of this small monograph represents a revision of several lectures given at a number of universities and adapted from the author's book on the physiology of the fetus, published in 1940. There is a selective bibliography of 48 titles and a good index. Even in these small monographs indexes are of value to reference librarians and research workers.

Simmonds' Disease: Extreme insufficiency of the adenohypophysis. By R. F. Farquharson, M.B., F.R.C.P. (C), professor of medicine and head of the department, University of Toronto, and physician-in-chief, Toronto General Hospital, Toronto. 8°, cloth, 93 pp., with 5 illustrations and 7 tables. Springfield, Illinois: Charles C Thomas, 1950. $2.00. (Publication No. 34, American Lecture Series.)

This monograph is based on a study of cases, in which the clinical and pathological features were described in useful detail, the patients finally being studied at post-mortem examination. The text is divided into a number of sections: diagnosis, pathogenesis and pathology, including the pathology of other endocrine glands and other tissues in the disease, the clinical picture, and treatment. A bibliography of 164 references concludes the text. There is a good index.

The Diagnosis of Salmonella Types. By F. Kauffmann, M.D., chief, International Salmonella Center, State Serum Institute, Copenhagen, Denmark. 8°, cloth, 86 pp., with 10 tables. Springfield, Illinois: Charles C Thomas, 1950. $2.25. (Publication Number 62, American Lecture Series.)

The scope of this monograph is limited to the methods used in the practical classification of the Salmonella group of bacteria by serologic and biochemical methods. The long list of all known Salmonella types should prove valuable to research workers in the field of bacteriology. There is a short bibliography, but the lack of an index detracts from the reference value of the monograph.

Some Relations between Vision and Audition. By J. Donald Harris, Ph.D., head, Sound Section, United States Naval Medical Research Laboratory, New London, Connecticut. 8°, cloth, 56 pp. Springfield, Illinois: Charles C Thomas, 1950. $1.50. (Publication No. 71, American Lecture Series.)

This small monograph discusses various physiologic aspects of vision and audition and compares them in sensitivity, intensities, energy integration, growth and decay of sensation, critical flicker frequency, bilateral interaction, single-nerve-fiber activity, intersensory facilitation and other factors. The text is concluded with a bibliography.

Medical Parasitology for Medical Students and Practising Physicians. By William G. Sawitz, M.D., associate professor of parasitology and associate in medicine, Jefferson Medical College of Philadelphia, and special consultant, United States Public Health Service, Communicable Disease Center, Atlanta, Georgia. 8°, cloth, 296 pp., with 90 illustrations. Philadelphia: Blakiston Company, 1950. $4.25.

This manual is for the use of students of the subject and is not intended to replace the larger works on medical parasitology. The approach is medical and not zoological. The material is well arranged and well illustrated with 89 drawings. There is a vocabulary of technical terms, and a good index. The publishing is good, and the manual should prove useful as a synopsis of the subject.

NOTICES

ANNOUNCEMENTS

Dr. William T. Haley, Jr., announces the removal of his office to 100 Atlantic Avenue, Marblehead.

Dr. Peter S. Zarecki, Jr., announces the opening of an office at 167 Maple Street, Springfield, for the practice of general surgery.

94TH INFANTRY DIVISION LECTURE

The next postgraduate medical lecture in the series presented by the medical units of the 94th (Bay State) Infantry Division will be held at the Boston University School of Medicine auditorium, 80 East Concord Street, Boston, on Tuesday, May 29, at 8 p.m. A discussion of recent investigations in the field of arthritis will be conducted by Dr. Henry Lemon, assistant professor of medicine, Boston University School of Medicine, Dr. Joseph Looney, chief of laboratories, Veterans Administration in Boston, and Dr. William H. Chasen, Chief of Arthritis Clinic, Veterans Administration in Boston. "The Last Glory," a World War II documentary film, will be shown.

BAY STATE HOSPITAL, INC.

The regular monthly meeting of the Bay State Hospital staff will be held on Thursday, May 31, at the home of David J. Calicchio, M.D., 9 Keswick Street, Boston, at 8:30 p.m. Dr. Aaron Feldman will speak on "General Practical Care of Cardiac Patients." A sound film, "Guide your Heart," will also be shown.

SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of June is as follows:

Saturday, June 2.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Seminar on Bacteriology in the Staff Conference Room.
11 a.m.–12 m. Seminar on Bacteriology in the Staff Conference Room.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds in the Staff Conference Room.

Thursday, June 7.
11:30 a.m. Allergy Conference in the Staff Conference Room.

Saturday, June 9.
9–10 a.m. Grand Surgical Rounds.
11 a.m.–12 m. Clinicopathological Conference in the Staff Conference Room.

Wednesday, June 13.
12:15 p.m. Psychosomatic Medicine Conference in the Staff Conference Room on the subject "Techniques in Psychotherapy." Dr. Calvert Stein.

Thursday, June 14.
12:15 p.m. Staff Meeting in the Staff Room.

Saturday, June 16.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Pathology Conference in the Staff Conference Room on the subject "Ovarian Tumors." Dr. Omar T. Pace and Dr. William Kaufmann.
11 a.m.–12 m. Medical Death Review in the Staff Conference Room.

Tuesday, June 19.
8:30 p.m. Group Conference in the Staff Conference Room on the subject "Review of Pathology in a General Hospital." Dr. William Kaufmann.

Saturday, June 23.
9–10 a.m. Grand Surgical Rounds.
11 a.m.–11 m. Surgical-Death Review in the Staff Conference Room.

Wednesday, June 27.
12:15 p.m. Pediatric Conference in the Staff Conference Room. Dr. H. H. Shuman.

NEW ENGLAND CARDIOVASCULAR SOCIETY

The Henry Jackson Lecture will be presented by the New England Cardiovascular Society on Monday, June 4, at 8 p.m., in the Boston Medical Library auditorium. Dr. Carl J. Wiggers, professor of physiology and director of the Department of Physiology at Western Reserve University School of Medicine, will speak on "Studies of Ventricular Contraction under Abnormal Conditions."
All interested persons are invited to attend.

AMERICAN HEART ASSOCIATION

The twenty-seventh annual meeting and the twenty-fourth scientific sessions of the American Heart Association will be held at the Haddon Hall Hotel in Atlantic City, New Jersey, from Wednesday, June 6, to Sunday, June 10.

PAN-PACIFIC SURGICAL ASSOCIATION

The Pan-Pacific Surgical Association will hold its Fifth Congress in Honolulu, November 7–19. All hotel and travel reservations should be made through the Association office, Suite 7, Young Hotel Building, Honolulu, Hawaii.

(*Notices concluded on page xix*)